U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE

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ORIGINAL

CLOZARIL AND SUICIDALITY

IN SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

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GRAND BALLROOM
HOLIDAY INN
2 MONTGOMERY VILLAGE AVENUE
GAITHERSBURG, MARYLAND

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MONDAY, NOVEMBER 4, 2002

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ATTENDEES:

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Other Participants:

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ATTENDEES: (Continued)

Other Participants:

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A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

(8:10 a.m.)

DR. OREN: Good morning. I'd like to call to order the meeting of the Psychopharmacological Drugs Advisory Committee of the Food and Drug Administration. My name is Dan Oren, and I'd like to welcome all the members of the panel and our guests, and we'll ask everyone on the panel, starting with Dr. Katz, to please go around and introduce themselves.

DR. KATZ: Russ Katz, Director of Neuropharm Drugs at the FDA.

DR. LAUGHREN: Tom Laughren, Neuropharm Drugs, FDA.

DR. COOK: Ed Cook, University of Chicago.

DR. WANG: Phil Wang, Harvard Medical School.

DR. HAMER: Bob Hamer, University of North Carolina.

DR. WINOKUR: Andrew Winokur, University of Connecticut Health Center.

DR. TITUS: Sandy Titus, FDA. I'm the Executive Secretary for Psychopharm.

DR. RUDORFER: Mat Rudorfer, National Institute of Mental Health.

DR. RYAN: Neal Ryan, University of

Pittsburgh.

MS. BRONSTEIN: Jean Bronstein, the public member.

DR. ORTIZ: Irene Ortiz, University of New Mexico.

DR. MALONE: Richard Malone, MCP Hahneman.

DR. MEHTA: Dilip Mehta, Industry Representative.

DR. TITUS: I'm going to read into the record the Conflict of Interest Statement for this meeting.

The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. All committee members and consultants have been screened for conflicts of interest with respect to the product at issue, competing product, and their sponsors. The reported financial interests have been evaluated and it has been determined that the interests reported by the participants present no potential for a conflict or the appearance of such at this meeting, with the following exceptions.

Richard Malone has been granted a limited waiver under 18 U.S.C. 208(b)(3) for his participation

as an advisor for a competitor. He receives less than $10,000. Under the provisions of the waiver, Dr. Malone will be allowed to participate in the discussions without voting.

Robert Hamer has been granted a waiver under 21 U.S.C. 355(n)(4) of the Food and Drug Administration Modernization Act for his ownership of stock in a competitor. The stock is valued from $5,001 to $25,000. Because 5 CFR 2640.202(a) de minimis exemption applies, Dr. Hamer does not require a waiver under 18 U.S.C. 208(b)(3).

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would like to note that Dr. Dilip Mehta is participating in this meeting as the non-voting guest industry representative.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any

current or previous financial involvement with any firm whose product they may wish to comment upon. Thank you.

DR. OREN: To begin our presentation this morning, I'd like to call on Dr. Katz, Director of the Neuropharmacological Drug Products Division at the FDA.

DR. KATZ: Thanks, Dan. I just really want to say welcome, thanks for coming. I think we've brought to you yet again another atypical, if I can use the word, issue. We're going to be asking you, as you know, to address the fundamental soundness of one particular study and, in addition, whether or not that study and whatever other information is available in toto support approval for the novel claim that the sponsor has proposed. So, I really just want to thank you in advance for your work, and I hope it's interesting.

There's one other point I want to make. As you know, we have issued to the sponsor an approvable letter for this application, which typically implies that with a few minor adjustments the application can be approved.

I would just urge you to not interpret that to mean that the definitive decision ultimately

about approvability/not approvability of the application has been made. We really are very interested to hear what you think about the data and whether or not they support either the proposed indication or some reasonably related indication.

So, with that, I'll turn it over to Tom Laughren, who will give you an overview of the issues we'd like you to consider. Thanks.

DR. LAUGHREN: Good morning. I'd also like to welcome everyone here to the meeting. The only topic for today is the supplement for Clozaril in the treatment of suicidality and schizophrenia and schizoaffective disorder.

(Slide)

I'd like to begin with giving a little bit of background to how we got to the InterSePT Study. As you're aware, the lifetime prevalence of suicide in patients with schizophrenia is roughly 10 percent, so it's a very big problem in this population.

Recently, we and other have done meta-analyses of clinical trials databases for the atypical antipsychotics. The reason for doing this meta-analyses was to try and determine if there was an excess risk of mortality from suicide in patients assigned to placebo as opposed to active drug. And as

you are probably aware, our meta-analyses and those of others have shown that these drugs, the atypicals, for the most part, are neutral with regard to suicide, suggesting that while these drugs have an effect on positive symptoms, there's no evidence, at least from the meta-analyses, that they have an impact on suicide.

So, given that background and an additional study that was done about five or six years ago that you'll hear more about, the ERI Study, which was basically a retrospective cohort study based on the Clozaril registry, in that study clozapine was greatly favored over other treatments with a risk ratio of 0.17, which is a very impressive outcome favoring clozapine. That, of course, was not a randomized study. But that was the start of our negotiations with the company to try and see if a prospective trial could be accomplished. And during those negotiations, we did reach agreement with the company that one adequate and well-controlled trial should be sufficient to support this new claim.

We also reached agreement on a two-year study comparing clozapine and olanzapine on the suicidality outcome, that is the InterSePT Study.

(Slide)

So, the study was done. The supplement was submitted in February of this year. The original claim that was sought in that supplement was for the use in the treatment of suicidality in patients with schizophrenia or schizoaffective disorder. And as you know, we issued an approvable letter for the supplement in August of this year.

(Slide)

Now, there are six issues other than the general question that we always ask you that we would like to have committee feedback on sometime during the course of the day. One issue is the potential for bias in the referral of events to the Suicide Monitoring Board. A second issue is simply the issue of adding a new claim focusing on suicidality in schizophrenia or schizoaffective disorder.

A third issue was the expansion of the Clozaril claim beyond the treatment resistant population for which it is currently limited. A fourth issue is the interpretation of the InterSePT Study with regard to olanzapine. A fifth issue is the adequacy of a single randomized controlled trial to support a new claim. And, finally, the adequacy of the suicidality outcome in the InterSePT Study. So I'm going to get into a little bit more detail about

each of these.

(Slide)

First of all, the question of bias. As you'll hear more about, Type 1 events are a critical component of the primary outcome for the study. Now, these events were confirmed in a blinded manner as being Type 1 events by a Suicide Monitoring Board. However, events that were to be considered by the Board were referred in an unblinded manner by psychiatrists at the sites.

The rate of confirmation of events that were referred was very high and essentially identical for both clozapine and olanzapine, 83 percent and 84 percent. So, there's a strong relationship between the number of events referred and the number confirmed. Therefore, it raises the question, since the events were referred in an unblinded manner, whether or not there might be bias in referring events.

(Slide)

So, we discussed this issue with the sponsor. They have some data that they think addresses it. FDA has also done its own independent audit to try and address this question, and Dr. Ni Khin, from the Division of Scientific Investigation,

is going to present her findings on their audit a little bit later in the morning. But, ultimately, we would like to have the committee's view on whether or not you think this issue of potential bias has been adequately addressed.

(Slide)

Next is the issue of a new claim that focuses on suicidality. Now, ordinarily, in the Psychopharm Group, we have not permitted sponsors to focus on what might be considered parts of a syndrome. For example, if a company wanted to get a claim for the treatment of hallucinations in schizophrenia, we would argue that that is pseudospecific, that of course the drug works for hallucinations, it also works for all the other positive symptoms.

So, one question that one might raise here is whether or not suicidality is just part of schizophrenia and shouldn't be teased out in some sense.

Now, obviously, we did issue an approvable letter, so the Division has taken a position on this that it is justifiable to separate this out, and our reasoning is that this is a serious event, and also there is a lack of evidence for effective treatments for this aspect of schizophrenia. But, again, this is

an issue that we need to have the committee's feedback on.

And in that regard, a major question for you is how should the claim be stated, if you feel that a claim is supported? Again, the company's initial proposal was to focus on the treatment of suicidality. This is the language that we proposed in the approvable letter: "Reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk for emergent suicidal behavior, based on history and recent clinical state".

So, again, part of the challenge to you is to help us try and articulate a claim, if you think a claim is supported.

(Slide)

Another issue is that if a new claim focused on suicidality were to be approved, this would clearly expand the use of clozapine beyond the treatment resistant population for which it is currently limited. Only about a fourth of patients in the InterSePT Study could be considered treatment resistant.

So, the question is do these data support -- and, of course, clozapine is not approved at all

for schizoaffective disorder. So the question is do the data support an expansion of the claim into this larger population?

(Slide)

Another question has to do with how the study should be interpreted with regard to the comparative drug olanzapine? One possible interpretation would be that this is evidence that clozapine is superior to olanzapine with regard to suicidality. Another possible interpretation is that olanzapine could be considered in some sense a representative member of the atypicals, and this is evidence that clozapine is superior to all atypical antipsychotics. Or one might do what we have done here, which is basically to take this as evidence that clozapine is effective for this particular clinical target. But, again, this is an issue mostly for labeling in how to describe the study in labeling, and how to describe the claim.

(Slide)

Another issue, of course, is this issue of whether or not one adequate and well-controlled trial is sufficient to support a claim. This, of course, is not the usual standard. Ordinarily, two adequate and well-controlled trials are needed to support a new

claim. There is, however, an alternative.

A single adequate and well-controlled trial along with confirmatory evidence is a standard that may be applied in certain situations. Now, the usual circumstance for applying this standard is if there is a single trial focused on mortality or irreversible morbidity, and replication is difficult for that reason.

A second possibility is that the single trial in question is so strongly positive -- either very small p-values or replication within that trial, because of positive findings at different centers, that there's a perception that there's no need to replicate it further.

So, the question, again, for the committee is is this standard appropriate for this particular situation?

(Slide)

And, finally, there is a question of the primary outcome in the InterSePT Study. Suicidality, as you'll hear more as the morning goes on, the were four events that fell under this definition of Type 1 events -- suicide, suicide attempt, hospitalization for suicidality, or need for increased surveillance for patients already hospitalized.

While clozapine was superior to olanzapine on this primary outcome, there was no actual effect demonstrated on completed suicides. The number was very small and it was roughly equal for both groups.

So, again, the question for the committee is in an absence of an actual finding on completed suicide, are these data sufficient to support a claim for suicidality.

(Slide)

The question that we need you to vote on is the usual one -- are the data sufficient to support a new claim? But, again, part of the challenge for you here this morning is to help us articulate the question, namely, if you think a claim should be supported, how should that claim be worded in labeling? And I'll stop there. Thank you.

DR. OREN: These are exceptionally interesting questions. To help us begin answering them today, I'd like to call on the Novartis presentations, beginning with Roy Dodsworth, Executive Director of Drug Regulatory Affairs at Novartis.

MR. DODSWORTH: Dr. Katz, Dr. Laughren, Dr. Oren, members of the committee, FDA staff, colleagues, guests, good morning. I'm Roy Dodsworth, from Novartis, and this morning I would like to guide

you through a journey of some ten years in the making, which culminates in our presentation to you this morning.

The journey relates to a rather unique clinical study that Novartis conducted in a high-risk population to assess the impact of Clozaril on reducing the risk of suicidal behavior, an important public health concern, and of particular significance to the psychiatric community.

Approximately 20 to 40 percent of schizophrenic patients will attempt suicide at least once during the course of their illness, and approximately 10 percent will ultimately die by suicide. This rate is probably even higher for schizoaffective patients.

(Slide)

Clozaril, known generically as clozapine, is an agent first developed during the 1960s and 1970s, and is generally considered to be the first atypical antipsychotic agent. It's a member of the dibenzo-diazopine class of drugs which work primarily on central dopaminogic and seratonogic receptors.

Clozaril was first approved in Austria in 1969, and was approved in the U.S. on September 26, 1989. It is currently approved in about 150 countries

around the globe, including Australia, Canada, and all members of the European Union.

The application that is subject of today's discussion was submitted to FDA on March 1st of this year, and was assigned a six-month priority review by the Division of Neuropharmacological Drug Products. It has since been submitted also in Australia and Canada, and will be submitted in the European Union later this month.

(Slide)

The current indication for Clozaril is for the treatment of severely ill schizophrenic patients who fail to respond adequately to other standard drug treatments for schizophrenia.

And the additional indication that we're seeking and which is the subject of your deliberations today is for reducing the risk of emergent suicidal behavior in patients with either schizophrenia or schizoaffective disorder who are judge to be at risk for suicide.

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This morning, we will present to you amongst all the information the results of InterSePT, the International Suicide Prevention Trial, a prospective, randomized comparison of Clozaril and

Zyprexa on their respective abilities to reduce the risk of suicide in a high-risk population of patients with either schizophrenia or schizoaffective disorder.

The study recruited patients generally excluded from other clinical trials, and encouraged investigators to do whatever was necessary to prevent suicide, maintain patient safety, and keep patients in the study.

Now, at the risk of repeating some of what Dr. Laughren said, we have had numerous discussions with FDA over the years, and this led ultimately to the design and execution of InterSePT Study.

(Slide)

In 1993, FDA asked us to assess the possible effect of Clozaril on mortality. This is the study by Walker and others conducted by a group at Boston University, which will be presented in greater detail in a few minutes by Dr. Meltzer.

From this assessment, we detected a possible signal that current Clozaril users seemed to have a reduced incidence of suicide and suicidal behavior, when compared to past users, based primarily on data from the Clozaril National Registry.

Following this finding, a report entitled "Mortality of People Using Clozapine" was published,

and this report formed the basis of a supplemental new drug application which the company submitted in 1995.

FDA subsequently issued a Not Approvable letter for this application primarily because it was a retrospective epidemiological analysis, but they expressed considerable interest in the outcome.

Given the significant nature of the suicide issue, FDA agreed with Novartis that a single prospective study which confirmed the reported observations and epidemiological signals would be sufficient for registering a new claim. Consequently, we embarked on a series of discussions with them, and this led ultimately to the design of the prospective study which we will present to you today.

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We've already submitted the final protocol for InterSePT Study to FDA in January of 1998, and initiated the study at some 67 centers in 11 different countries shortly thereafter. We completed it early last year, and along the path which led us here today, we participated in numerous discussions with FDA regarding the study, the statistical analyses, the results, and your review of our application. In fact, we submitted a draft report to FDA in December of last year, and filed a supplemental application requesting

a new indication on March 1st of this year.

Consistent with the industry goal for priority review drug, FDA rendered it approvable in a letter to us dated August 30, this year, but that letter also sought answers to several questions, many of which Dr. Laughren just outlined to you, and which have been provided to you in your briefing book.

We have since responded to all outstanding questions, and today FDA is seeking your guidance and counsel on several issues.

(Slide)

To that end, we have two objectives today. The first is to seek your agreement that reduction in risk for suicidal behavior in this population represents an important health issue that could clearly represent a new indication for a drug that is shown to possess such activity.

The second is to present the results of InterSePT, a prospective randomized controlled study designed to assess precisely that for Clozaril. It is our belief that the results of InterSePT, when taken together with the other published reports and available information, represents a significant body of evidence demonstrating that Clozaril does, in fact, reduce the risk of suicidal behavior in high-risk

populations, and that Clozaril should be so indicated.

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Therefore, let me please introduce our program to you today. Dr. Herbert Meltzer, from Vanderbilt University, will present an overview of suicidal behavior as a public health issue, along with some of the background data which led up to the design and execution of InterSePT. This will include a review of the epidemiological study carried out by Walker and others that evaluated Clozaril and suicide.

Dr. Rocco Zaninelli, Executive Director of Clinical Research and Development for Neuroscience at Novartis, will then present the InterSePT results themselves.

Dr. Ranga Krishnan, Chairman and Professor of Psychiatry and Behavioral Science at the Duke University Medical Center and Chairman of the independent Suicide Monitoring Board, will speak to the role of that board in the conduct of the study. The SMB made all primary endpoint decisions in a blinded fashion independent of the Principal Investigators in the study.

Finally, Dr. John Ken, Chairman of the Department of Psychiatry at the Zucker Hillside Hospital and Professor of Psychiatry, Neurology and

Neuroscience at the Albert Einstein College of Medicine, will summarize the benefit/risk assessment for Clozaril as an agent to reduce the risk of suicidal behavior in high-risk populations.

Allow me then, please, to introduce next on the agenda, Dr. Herbert Meltzer. Dr. Meltzer is Bixler Professor of Psychiatry and Pharmacology at Vanderbilt University of Nashville, and he will speak to suicide behavior as a public health issue, as a domain separate from psychosis, and the data that preceded and gave rise to InterSePT. Dr. Meltzer.

DR. MELTZER: Thank you very much, Mr. Dodsworth, and I'd like to thank Novartis and members of the committee and the FDA staff for the opportunity to speak to you today about this issue. It is particularly a personal pleasure since my role in research on the possible effect of Clozaril on suicidality led to InterSePT.

(Slide)

The presentation that I will give will discuss suicidal behavior in schizophrenia and schizoaffective disorder. The evidence of suicidal behavior is a separate domain of behavior from psychosis because that's a key part of the story to determine whether or not suicidality could be the

object of a specific therapeutic intervention and whether it could be a separate indication for Clozaril.

And, finally, I'll present the evidence which existed prior to InterSePT, which suggested that Clozaril reduces the risk of suicidal behavior in patients with schizophrenia and schizoaffective disorder, and led Novartis to accept my suggestion for a study which eventually became InterSePT, with the help of the FDA.

(Slide)

From the beginning of awareness of the concept of schizophrenia as a syndrome, there was evidence that suicidality, suicidal behavior, was a serious problem. Emil Kraepelin, in the textbook from 100 years ago which launched psychiatry, indicated his awareness of the potential for violence to self and others in what he called "dementia praecox" by the quote that you see there -- "Patients with dementia praecos often need hospitalization to prevent aggression against others and suicide".

Some 14 years later, Eugen Bleuler, who gave schizophrenia its current name, identified suicidal behavior as "the most serious of schizophrenic symptoms", reflecting that it must have

been very common in his era as it is now. And I think many of us remember that David Satcher, a few years ago, when he was Surgeon General, made the problem of suicide and mental illness in general one of the major focuses of his tenure.

(Slide)

Suicidal behavior should be thought of as a spectrum of behaviors. At one end of the spectrum are suicidal thoughts and suicidal plans which we must rely upon patients or their significant others to communicate and, unfortunately, they often do not do that.

At the other end of the spectrum are suicide attempts and completed behaviors, which are usually, but not always, apparent to observers. I think we are all aware that many suicide attempts and even completed suicides go unnoticed and unreported, in part because of the stigma associated with suicide.

There are numerous studies from all over the world, some of which are cited below, which report that 20 to 40 percent of patients with schizophrenia and schizoaffective disorder attempt suicide, and recent studies from Scandinavia indicate the rate is increasing in direct proportion to the decrease in the availability of hospitalization for schizophrenia, and

declining days per hospitalization.

As Dr. Laughren mentioned, approximately 10 percent -- the range in various studies is 4 to 13 percent -- of people with schizophrenia and schizoaffective disorder complete suicide. It remains the leading cause of death in schizophrenia up to age 35, and it persists thereafter even into later life.

According to Surgeon General Satcher's report in 2001, the annual number of suicides in the United States is 3600, and that's quite probably an underestimate because of the reluctance of medical examiners to identify suicide as the cause of death.

(Slide)

I will now discuss some of the evidence that suicidal behavior is a separate domain of psychopathology and does not follow strictly from psychosis.

(Slide)

There is considerable evidence that the control of positive symptoms alone does not provide optimal control of the risk for suicide. Dr. Laughren mentioned from the meta-analyses that Kahn, (phonetic) et. al. published, that even though the other atypical antipsychotics were very effective to control positive symptoms, they did not differ from placebo or typical

neuroleptics in the rate of suicide. And, indeed, every major review of the effect of typical neuroleptic drugs on the rate of suicide following introduction in the 1950s not only did not find any sign of a decrease in the rate of suicide, but there were a number of early indications that the rate actually increased and this was attributed to the more suicidal patients being specifically treated with typical neuroleptics.

In the study that I will review, the Meltzer Okayli study, that foresaw a similar but causally reduced suicide, we studied a large number of neuroleptic-resistant patients with persistent positive symptoms, and a smaller but still significant number of neuroleptic responsive who differed dramatically in the incidence or persistence of psychotic symptoms, and both the lifetime and current rates of suicidality in those two groups were indistinguishable.

(Slide)

I'd like to speak to the issue of suicidal behavior in schizoaffective disorder versus schizophrenia. These data from our Mental Health Clinical Research Center were patients who were diagnosed on the basis of structured interviews, and

I think it's fairly reliable, and they are very consistent with the rest of the literature comparing these two groups.

And you can see, looking at a lifetime never reporting suicidal -- part of the suicidal spectrum here, we had 40 percent of the group in schizophrenia, 10 percent of the schizoaffective -- very small number -- no difference in suicidal plans, but the attempt rate was, as would be expected, are consistent with most of the literature on schizophrenia are 40 percent, and up to 70 percent in the schizoaffective. And the literature again is very consistent that the means by which people with schizoaffective disorder attempt suicide is much more often violent and more likely to be lethal.

(Slide)

This slide provides additional data, looking now at psychopathology, on the relationship between lifetime suicidal behaviors and various types of psychopathology. The data are very similar when you look at current, and what we see here is that a very high correlation between a Hamilton-Depression Total score at the time of assessment, or the BPRS-Anxiety/Depression subscale, and the suicidal history of these individuals.

When we look at the current positive or negative symptoms and the more global measures of quality of life, this is the Heimler (phonetic) Carpenter scale, or the Global Assessment of Function Scale, you can see negligible correlations.

(Slide)

Now, the burden of suicidal behavior probably -- it's so important it needs to be mentioned, but I'm sure all of us are aware of it. It falls not only on individual patients, but also on their family and society.

Unsuccessful suicide attempts may lead to permanent physical impairment, as from a gunshot wound or an overdose which produces organ damage. It may also leave long-lasting psychological scars not only on the patient, but their families. Serious suicide attempts will undoubtedly disrupt the daily lives of patients and their families.

Obviously, this has big financial implications for the individual, for society which bears the burden of paying for the problems with schizophrenia. Palmer, et. al. estimated the average cost of a suicide attempt at $33,000 a year, mainly due to the cost of hospitalization. Indeed, today, hospitalization for suicide attempts or to prevent it

may be among the very most common reasons for hospitalization of schizophrenia.

(Slide)

I'd now like to briefly review the evidence that Clozaril reduces the risk of suicidal behavior.

(Slide)

I'm going to start with the mirror image study which Dr. Okayli, who was then a psychiatric resident, and I did at Case Western Reserve University. The impetus for that was my clinical observation that the number of times I was dealing with a problem of suicidal behavior in the patients I was treating with Clozaril was dramatically less than what I had come to expect in the same setting over a dozen years with similar types of patients.

The led us to do a very careful retrospective study of 88 consecutive patients, interviewing the patients again, their family members, and obtaining all available medical records as to the history of suicide in the two years before we began treating them with Clozaril. And we had prospective data. We had monthly ratings of suicidal behavior during the entire course of this study.

Patients were mainly treated

with Clozaril monotherapy. During this time, everybody was seen weekly. We did offer a psychosocial treatment program which would impact, of course, on the interpretation of the results.

(Slide)

This is the major result of that study. What we found was that the group as a whole -- 53 percent of them reported no suicidal behavior from that whole spectrum that I talked about in the two years before Clozaril, and that increased to 88 percent in the follow-up period.

Suicidal ideation, again, collected prospectively, did not change. Accident or unintended self-harm which were mainly due to command hallucination decreased dramatically. And the major finding was the number of low and high probability suicide attempts decreased dramatically. There were only 3 low probability attempts, all within the first few months of treatment with Clozaril, which you'll see an echo of that when you look at the Clozaril-Zyprexa comparison. It apparently takes some time before the optimal benefits of Clozaril are manifest.

And we published these data in the American Journal of Psychiatry along with some others which I'll mention in a moment, and it stimulated a

number of followups.

(Slide)

At the time we looked at the Clozaril National Registry which did have a report on completed suicides, and as of '94 -- the annual expected rate in the United States would be about 0.2, it was about 0.05 percent in '94, looking at the Clozaril National Registry. William Reid, the Commission on Mental Health in Texas, did a similar review in 1998, and found even a greater discrepancy from the expected rate.

Dr. Reid also compared the rate in all of Texas, from their records, for all mental health patients treated with Clozaril versus the ones not treated with Clozaril, and found almost an identical decrease in that subsample in terms of lower rates of completed suicide on Clozaril, and Rob Kulan's (phonetic) group at the Modsley (phonetic) looked at the U.K. Clozaril Registry, comparing it with a series of papers published in the 1990s from the United Kingdom on completed suicide and schizophrenia, and found again virtually the same reduction that everybody who has looked at this has found, and there have been a number of other subsequent replications of that.

(Slide)

Now I'd like to go into some detail which I know the committee was requested about this Walker study. The Walker study was an epidemiologic study connected by the Rothman (phonetic) group, a very respected group of epidemiologists, from Boston University.

(Slide)

The purpose of the study was actually to determine the mortality from all causes associated with the use of Clozaril, something that the FDA was very keen on because of the possible increased rate of pulmonary embolism of Clozaril.

The study examined mortality in all patients who had received Clozaril in the United States from its approval in 1989 until the end of '93. The main analysis in the paper and the data that I'll share with you was on the subgroup who were between the ages of 10 to 54, leaving out the group with Parkinson's Disease who were treated with Clozaril because of aldopapsychosis (phonetic) and who had a very separate mortality experience.

There were 67,072 current and former Clozaril users who constituted the sample, and they had a total exposure of 85,399 years.

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The group was divided into three groups. The first group were people who were currently still taking Clozaril, as indicated by the fact they had had a white count reported to the Registry within the last two weeks by the end of 1993.

Recent users had recently discontinued sometime between 15 and 106 days, and the third group were those that had discontinued even a longer period of time. So, everyone in the sample had received Clozaril at some time.

Of course, the mortality data that had been reported to Novartis during this period, but there were other data which could be obtained from the National Death Index and the Social Security Administration Death Master Files by cross-linking Social Security Numbers, initials, age, sex, race, et cetera.

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This is the key summary slide of that. The death due to suicide in the currently still taking Clozaril group was a rate of 39 per 100,000 person-years. The mortality due to suicide in the recent and past groups were 246 and 221 per 100,000. These are well within the range reported for the population of

people with schizophrenia as a whole. There is no signal in these data that having recently been on Clozaril, that the rate increased in relationship to the discontinuation. In fact, they did a special analysis, a very important part of that paper, in which they looked at the people who had been discontinued due to agranulocytosis, and they compared the rate in that group -- which wouldn't be biased by any possible stop in the medication because they were suicidal -- and that group did not differ from the rest of the group, indicating that the rest of the group was not particularly biased due to suicidal behavior as a reason for discontinuation.

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And when they looked -- again, the primary purpose was all causes of death -- there was a strong signal that Clozaril reduced the overall mortality, and that that overall mortality decrease was due to the lower rate of suicide. So, the current Clozaril users had a 54 percent lower risk of death from any cause than the past Clozaril users -- this is the 95 percent confidence limit -- does not overlap one, whereas the recent users were slightly elevated compared to the past users.

The suicide, as Dr. Laughren mentioned,

showed a hazard ratio of .17, a reduction of 83 percent, which is the exact same range that all the other studies that I've mentioned have always come up with. And we saw a slight increase, again, in the recent users.

Suicide accounted for 19 percent of all the deaths in the sample, mainly in the recent and the past users.

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So, these are the conclusions from Walker, et. al.m that Clozaril reduced the risk of completed suicide, that their findings were consistent with the previous finding, that the reduced suicide rate was the largest contributor to the lower overall mortality rate in the Clozaril current user group, and that the beneficial effects of Clozaril on suicide did not persist after it was discontinued.

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So, let me summarize with the key points that I hope I have made during this talk: that attempted suicide is a very important public health issue, occurring in at least 20 to 40 percent of patients with schizophrenia and schizoaffective disorder; attempted suicide is a major burden on patients, families, and society; that suicidal

behavior is a separate domain from psychosis -- antipsychotic drug does not necessarily mean antisuicide drug; extensive previous research suggests, but does not prove -- clearly, there are many problems with Okayli and others in terms of evidence-based medicine -- but they did suggest that Clozaril reduces suicidal behavior.

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And so the stage was set for InterSePT, which was designed by a number of people to provide a controlled, prospective test of the hypothesis that Clozaril reduces the risk of suicidal behavior, and Dr. Rocco Zaninelli, who is the Executive Director for Clinical Research and Development at Novartis, is going to present it. We think you'll see that it's an innovative design directed toward an extremely important public health problem in a very high-risk population. Thank you very much.

DR. ZANINELLI: Thank you, Dr. Meltzer. Good morning. Dr. Meltzer has discussed the scientific findings which led to the development of InterSePT. I will now present the detail of the design and the results of the study.

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My presentation today include a statement

of the objective of InterSePT, a discussion of the study design, a component of which is the independent Suicide Monitoring Board. Within that presentation, Dr. Krishnan will elaborate on the role of the Suicide Monitoring Board. I will then address the statistical methods and the efficacy and safety results of InterSePT. In response to a request from the FDA, I will also present a review of the process of referring cases to the SMB. Finally, I will draw some conclusions from the InterSePT results.

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The study title, which you have seen a couple of times already, is also a statement of the objective of InterSePT. InterSePT was a prospective, randomized, international, parallel-group study for comparison of Clozaril/Zyprexa in the reduction of suicidality in patients with schizophrenia or schizoaffective disorder who are at risk for suicide.

InterSePT was an open-label study, however, specific assessments were carried out by clinicians blinded to patient identifiers, patient treatment specifically.

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I will now describe the study design.

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The schematic you are about to see illustrates the study design of InterSePT. Patients were randomized to either Clozaril/Zyprexa for a duration of two years. The initial four weeks were the transition phase, during which patients discontinued their previous antipsychotic medications while beginning the assigned study medication.

Patients randomized to Clozaril started at 12 mg BID, patients randomized to Zyprexa at 5 mg once a day. The recommended dosage ranges were 200 to 900 mg per day for Clozaril, and 5 to 20 mg per day for Zyprexa. These ranges correspond to the dosage ranges for each of the medications in the 11 countries participating in InterSePT. There was no fixed dose for any length of time during the study.

For the first 26 weeks of the study, the patients received weekly intervals. This schedule corresponds to the necessity to monitor the white cell counts in the Clozaril patients. The visit frequency was the same in the Zyprexa group. So the frequency and duration of contacts in both groups with site staff was the same. Whereas the Clozaril patients blood drawn for the WBC counts at the contacts, the Zyprexa patients had vital signs taken.

After 26 weeks, the visit frequency for

both treatment groups became biweekly, again, corresponding to the required monitoring frequency for Clozaril patients.

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InterSePT included patients with schizophrenia or schizoaffective disorder recording the DSM4 criteria who were at high risk for suicide. Patients needed to satisfy at least one of the following criteria: A suicide attempt within the last three years; had hospitalization to prevent suicide in the last three years; moderate to severe suicidal ideation and depression within one week of the baseline assessment; or moderate to severe suicidal ideation and self-harm command hallucinations within one week of baseline assessment.

Many patients included in InterSePT met two or more of this criteria, thus confirming this was an at-risk population. The inclusion of a population at risk for suicide influenced other inclusion and exclusion criteria. For example, patients with a prior history of substance abuse or drug abuse were not excluded from the study. More importantly, in keeping with the medical mandate to prevent suicide and maintain patient safety, there were no constraints regarding the use of concomitant medication use during

the study.

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The choice of the comparison medication was deliberate. Preliminary to the design phase of InterSePT, the use of placebo in this patient population was considered unethical and medically inappropriate. Zyprexa was chosen because it is an atypical antipsychotic that is pharmacologically similar to Clozaril. A previous study by Tran, et. al. had demonstrated a lower rate of adverse events related to suicidal behavior among patients treated with Zyprexa compared to patients treated with Risperdal.

Zyprexa is effective in treating psychosis. It is generally well tolerated. Finally, it was available in all of the countries wanting to participate in InterSePT.

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The rational for the open-label design was based on the assumption that any attempt to blind the study would be compromised by at least two factors, one factor being the need to monitor white blood cell counts in the Clozaril patients, the other the clinical fact that Clozaril and Zyprexa have fairly distinct adverse event profiles, that it would be

difficult to blind the medications from experienced clinicians.

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The primary efficacy endpoint for InterSePT was a Type 1 or Type 2 event. I will define these types of events before describing the statistical methodology which was used to analyze the results.

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A Type 1 event was defined as a significant suicide attempt or hospitalization due to imminent suicide risk, including a increased level of surveillance in patients already hospitalized. The data concerning such events were assessed by the Principal Investigator at the site, and confirmed by the Suicide Monitoring Board.

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A suicide attempt itself was defined as actions committed by a patient either with willful intent or as a response to internal compulsions or disordered thinking that put him or herself at risk for death.

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A Type 2 event was defined as a worsening of suicidality as measured by a score of 6 or 7 on the

Clinical Global Impression of the Severity of Suicidality related by a Blinded Psychiatrist, or CGI-SS-BP. However, a level of 6 or 7 indicates a score of much worse or very much worse. This scale is a modified version of a Global Improvement Scale of Clinical Global Impression, which is a standard assessment in psychiatric research. The blinded psychiatrist performing the reading was at the site, but was not otherwise involved in the conduct of the study.

Type 2 events also included an implicit worsening of the severity of suicidality as indicated by the occurrence of a suicide attempt or hospitalization to prevent suicide. That is, every Type 1 event was also a Type 2 event. Every Type 1 event was therefore considered in two dimensions, the behavioral aspect -- the suicide attempt or hospitalization to prevent suicide, which was the Type 1 event -- but also in the implicit worsening which is associated with suicidal behavior.

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There are also a number of secondary efficacy assessments, the CGI-SS-BP, besides comprising a component of a primary endpoint, overall changes from baseline in a CGI-SS-BP were also

recorded as a measure of the clinician's impression of changes in the patient suicidality status.

The InterSePT Scale for Suicidal Thinking as rated by the Blinded Psychiatrist is a new scale which was especially developed for InterSePT. It is based on an adaptation of Scale for Suicidal Ideation. It has been validated for the InterSePT population.

Three scales were used to assess syndromal psychopathology, depression, and anxiety, respectively: The Positive and Negative Syndrome Scale, the PANSS, the standard measure in studies of schizophrenia and schizoaffective disorder; the Calgary Depression Scale, which was specifically developed to measure depression syndrome in schizophrenia; and the Covi Anxiety Scale, which is a standard measure of anxiety.

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A crucial aspect of InterSePT was the determination of Type 1 events for the independent Suicide Monitoring Board, concerning which Dr. Krishnan will speak to you in a few moments. I wish to describe in this schematic the overall process by which data flowed to the Monitoring Board.

Patients in this study were cared for at the site where all unblinded clinical assessments were

made. The blinded psychiatrist, as mentioned already, was also at the site. Information collected from the site during the study was forwarded to the Medical Monitor at the Inginex Pharmaceutical Services, the research organization responsible for conducting InterSePT. The Medical Monitor was a trained psychiatrist, whose main functions were to oversee the quality of data flowing to a database but, more particularly, to blind all information pertaining to suicide attempts, suicides, and hospitalizations to prevent suicides -- that is, potential Type 1 events.

The case information was then passed on to an Independent Suicide Monitoring Board which deliberated the case and made a determination of whether the data actually constituted a Type 1 event or not. The results of the SMB's deliberations were passed back to Medical Monitor. The data concerning these events were entered into the database.

Dr. Krishnan, who is Chairman of the Suicide Monitoring Board, will now present the details regarding the work of the SMB. Dr. Krishnan?

DR. KRISHNAN: Thank you, Doctor. It's nice to discuss the role of the SMB with the members of the Advisory Group.

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Let me very briefly tell you who we were and what we did. The SMB consisted of three individuals -- myself, Isaac Sakinofsky. He is Professor Emeritus at University of Toronto. His clinical work is on suicide in schizophrenia, and his clinical research is also focused in this area.

The third individual is Hannele Heila. Hannele Heila is an individual who conducted on of the largest psychological autopsy studies of suicide in the context of schizophrenia.

The three of us were not affiliated to any of the investigative sites. The membership remained constant throughout the trial, and each member participated in all the meetings and in all the decisionmaking for all the individual events.

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The primary role of the SMB was to evaluate all the relevant data to determine whether a Type 1 event occurred. So, we evaluated all deaths and determined if the cause was suicide; potential suicide attempts we evaluated to determine their potential lethality; and hospitalizations related to suicidal behavior were assessed to see if the hospitalization was due to imminent risk of suicide and not due to other reasons such as increased

psychosis, worsening of psychosis, et cetera.

Let me briefly give you an idea of the thought process that went into making some of these decisions. If you review the literature in the context of assessing suicide, it is clear that while it is possible to delineate historical and current risk factors for suicide in samples of patients, when you try extrapolating it to the individual, these data are suggestive but are not definitive. So, essentially they yield either too many false-positives or they fail to identify many of those who later turn out to be at risk for suicide.

The Suicide Monitoring Board, therefore, fell back on careful considered clinical judgment tested and tempered by teleconferences that had any conflicting opinions and drew reasoned consensus from the group, sometimes with the aid of additional information requested about the event and about the patient.

The key to evaluating the important behavioral phenomenon turned on assessing the seriousness of the suicidal intent and the driving force behind it. In this context, it is useful to distinguish between intent that is subjective -- in other words, not always that which is explicitly

stated by the individual, or objective intent which is implicit in the circumstances of the event. Objective intent is evaluated by evidence of preparation, choice of the method of attempting suicide, and by any steps taken to prevent the act being plotted by this.

The clinician and, in this case, the Suicide Monitoring Board, had to estimate the degree of trust that can be placed in a patient's statement of intent in both directions, i.e., that the patient will or will not kill him or herself. Patients are well known, for example, to threaten self-harm for the sake of some gain, such as admission to the hospital. On the other end, the seriously suicidal person is likely to deny or conceal intent, but suicide will not be prevented.

And, further, where an individual is in the midst of a psychotic episode, they do not always follow logical process. For instance, lethality of an attempt may not follow the degree of intent in either direction. This can account for the fact and the frequent finding that suicide victims were not perceived as at risk for suicide at their last clinical appointment. At the same time, buffering and mitigating factors also have to be considered, namely, where do they live? What is their willingness to

live? What is the circumstances in their life that at that point makes them either more likely or less likely to attempt suicide.

So, we had to consider all these factors and try to arrive at reasoned judgment as far as possible in making a decision whether they met criteria for one of those events by events that we discussed.

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What were the material that we utilized? There was a bunch of case report forms which is a suicide attempt form, the rescue intervention form, the Calgary Depression Scale, the InterSePT Scale, and we also looked at all the clinical reports from the charts and history of suicidal behavior. Remember, all these charts were carefully evaluated prior to our seeing them, to take out any information that is there about diverse experiences, any clue about what the drug was, et cetera, so everything which was connected to that was blacked out and sent to us. So, the information that we had was essentially anonymized as to which compound or which drug the individual was receiving.

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We reviewed 577 events, and we determined

483 to be Type 1 events, of which 111 were suicide attempts and 372 were hospitalizations to prevent suicide.

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In conclusion, I just wanted to emphasize a couple of things: Members were independent of any of the sites, that the review was blinded, and the classification of each event was on a pre-determined and pre-defined process, and the determination of Type 1 events were unanimous.

Let me just also briefly say one word. When we evaluated in the context of the Suicide Monitoring Board, what we actually got was stories of patients, and these stories were compelling. Here you are talking about a group of individuals who are generally excluded from most clinical trials. They were very, very ill. And the stories were striking. The number of attempts, the degree of co-morbidity with other problems, the lack of support systems very often in this group of patients, and the level and the chronicity of their illness during the time frame when they participated in the study and the time frame before they entered the study, and you can see to some extent from the type of events that occurred during the study and prior from the study, everything from

jumping off bridges, trying to hang themselves, overdoses, et cetera. And so one has to think of this in the numeric sense, in the statistical sense, I think it is also important to keep in mind the nature of this patient population that was evaluated and studied. Thank you.

DR. ZANINELLI: Thank you, Dr. Krishnan. I will now continue my presentation by turning to the statistical methods which were used to analyze the data from InterSePT.

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The primary efficacy analysis of InterSePT was a time-to-event analysis based on the approach of Wel, Lin and Weissfeld, the WLW method. This method is used to analyze time-to-multiple-event data. It allows the combination of different types of events into a single dataset, which was the case in InterSePT with the combination of Type 1 and Type 2 events. The WLW method provides an overall test of the difference between treatments. In the case of InterSePT, the difference between Clozaril and Zyprexa, with regard to the risk of experiencing a Type 1 or Type 2 event.

The WLW method was established as the primary efficacy analysis by protocol amendment. The regional InterSePT design designated only the Type 1

event as the primary endpoint, however, there was a concern there may be too few events of suicidal behavior in the course of a study in which the emphasis was on patient safety and the prevention of suicide. Therefore, the Type 2 event, which was reported to reflect more implicit suicidal behavior was introduced into the design.

The use of the WLW method was agreed to by the FDA during deliberations on the design of InterSePT.

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A number of supportive analyses were also conducted. The Cox proportional hazards analysis, which included in the model the factors of drug treatment, number of suicide attempts, current substance or alcohol abuse, country grouping, gender, and age.

Kaplan-Meier estimates of cumulative probabilities were also conducted. And, finally, analysis of clinical variables were carried out based on analysis of the last-observation-carried-forward dataset.

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The statistical assumptions behind the sample size calculation were as follows: the

randomization was set at 1-to-1; the log-rank test established alpha at 5 percent, with power at 80 percent. It was estimated that 45 percent of Clozaril patients of 55 percent of Zyprexa patients would have at least one Type 1 event during the two-year observation period. Therefore, a total 381 events would be necessary to distinguish a difference. With a frequency of 50 percent, at least 762 patients were needed for the study. And allowing for a 15 percent dropout rate, about 900 patients needed to be randomized to study medication.

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Finally, getting to the results of the study, I'll start off with the characteristics and disposition of the study population.

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InterSePT was conducted at 67 centers in 11 countries. The first patient was enrolled in March 1998, last patient visit took place in February 2001, the database was locked in June 2001.

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In total, 1,065 patients were screened, and most of those patients were actually randomized and started medication. The intend-to-treat population consisted of all randomized patients, 490

in each group. Approximately 98 percent of these patients actually received medication and, of these, about 61 percent completed the two-year observation period.

Of the 40 percent who discontinued the two-year observation period, 15 percent in the Clozaril group and 18 percent in the Zyprexa group, still contributed complete data to analysis at the primary endpoint, either by having a Type 1 or Type 2 event before or after discontinuation.

The study design included the stipulation that patients who dropped out would be, as much as possible, followed to their individual two-year endpoint to determine whether a Type 1 or Type 2 event occurred after discontinuation. These were so-called "retrieved dropouts".

The number of true dropouts -- that is, patients who had no event prior to discontinuation and were ultimately lost to followup -- was, therefore, 24 percent in the Clozaril group and 80 percent in the Zyprexa group. One of the conclusions of this is that about 80 percent of the patients in each group contributed complete data for the analysis of the primary endpoint.

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The distribution of age was similar across the two treatment groups. The mean age of onset of the disorder was about 24 years; median duration of illness, ten years. The percentage of males and females was similar across treatment groups. You can also see that the distribution of race was even in both groups.

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Looking now at diagnosis at baseline. This is about 60 percent of the patients were diagnosed with schizophrenia and 40 percent of the patients in each treatment group were schizoaffective disorder. Around 27 percent of the patients in both groups were classified as being treatment-resistant by history. This percentage was based on historical information from the patient's files, and not on the strict application of criteria for treatment resistance.

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Turning now to the psychometric scores. At baseline, we see that the severity of suicidal behavior at baseline as measured by the CGI-SS-BP was 2.2 in both groups. This corresponds to a rating of mild to moderate severity of suicidality. The mean number of lifetime suicide attempts, the mean number

of lifetime hospitalizations to prevent suicide was greater than 3 in both groups. These numbers underscore the fact that it is a high-risk population.

For both groups, the mean total score on the PANSS was above 80, indicating that although most of these patients were receiving antipsychotic medication before the trial, there was still a substantial degree of psychopathology present at baseline.

On the Calgary Depression Scale, a score of around 10 indicates mild to moderate levels of depressive symptomatology and, finally, Covi Anxiety score of around 4 indicates rather low level of anxiety.

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For those patients who discontinued the study, the most frequent reason for discontinuation was withdrawn consent, followed by discontinuation due to adverse events. For most of the reasons we see here, the proportion of patients that discontinued treatment was similar across the two groups. There were a few differences. Three patients in the Clozaril group, none in the Zyprexa group, discontinued because of abnormal lab values or procedure results, while 6 patients in the Zyprexa

group and none in the Clozaril group discontinued due to unsatisfactory effect on the suicide risk.

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With regards to study medication, the mean dosage for Clozaril during was 274 mg, if it was Zyprexa, 17 mg, so overall during the study. For Clozaril, the mean dosage beginning in month 4, that is following the titration period that's customary for Clozaril, the mean dosage is about 225 mg per day.

The dosage for Clozaril patients ranged from 13 to 725 mg per day, from which we can deduce that no Clozaril was dosed at the ceiling of the recommended range. For Zyprexa, the actual dosing range was 3 to 41 mg, with about 18 percent of the patients receiving doses in excess of 20 mg per day.

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I will now present the results of the analysis at the primary endpoint, which was again the time to first Type 1 or Type 2 event.

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These bar-graphs represent the distribution of Type 1 events -- that is, suicide attempts and hospitalizations to prevent suicide in the two treatment groups.

Overall, 102 patients in the Clozaril and

141 patients in the Zyprexa group had a Type 1 event. The suicide attempts and hospitalizations to prevent suicide, you see there are 34 suicide attempts in the Clozaril group, 55 in the Zyprexa group; hospitalizations, 82 in the Clozaril group, 107 in the Zyprexa group. These numbers, 34 of each, don't add up to 102 because there were patients who had a suicide attempt and a hospitalization in both groups.

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This slide shows the distribution of patients in the treatment groups and the number of Type 1 events they had. You see that most patients in each of the treatment groups had only one event -- this is the number of patients. But there were not a few patients who had more than one Type 1 even during the course of the study. In each of these cases, there were more patients in the Zyprexa group than in the Clozaril group.

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This slide shows the distribution of Type 2 events across the treatment groups. We'll review the definition of Type 2 again. Type 2 events encompass a worsening of suicidality on the CGI-SS-BP as well as a worsening implied by the occurrence of Type 1 events, suicide attempts or hospitalizations to

prevent suicide.

So, with that in mind, look at this. The Clozaril group, there were 120 patients who had a Type 2 event, in contrast to 161 in the Zyprexa group. However, 102 of these events were actually the Type 2 events we saw two slides previously in the Clozaril group. These 141 we also saw two slides previously, that is, the preponderance of the material making up the Type 2 event was actually the Type 1 event. This result needs to be kept in mind when you consider the further results in the analyses I'm about to present.

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The results of the primary efficacy analysis using the WLW method indicates a significant difference between the groups in favor of Clozaril, the p-value being .031. The results of the supporting Cox Proportional Hazard analysis show ratios of .74 and .76 for Type 1 and Type 2 events, respectively, a ratio of greater than 1 would be in favor of Zyprexa or a ratio of less than 1 in favor of Clozaril. The differences for both types of events were statistically significant. You see here the p-values, .021 and .026 for Type 1 and Type 2 events, respectively. The mean result here that for the Clozaril group relative to the Zyprexa group there was

a reduction of risk of 26 percent in the Clozaril group relative to the Zyprexa group, reduction of risk for suicide attempt or hospitalization to prevent suicide.

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Look now at the Kaplan-Meier plots, you can observe the cumulative probabilities of a Type 1 event were 24 percent in the Clozaril group and 32 percent in the Zyprexa group. The probability estimate is fairly constant for Clozaril of about 22 to 24 percent from about month 12. Confirming results of the Cox analysis, this represents for the Clozaril group a 25 percent reduction in the probability to have a Type 1 event.

What this means clinically can perhaps best be shown from the time point at which the Clozaril patients have a 24 percent probability, which is around 12 months or so. This indicates that the acuity benefit accruing to the Clozaril patients is amplified during the second year of the study.

The Kaplan-Meier plot for Type 2 events is very similar, which is not surprising considering that the data involved in this analysis are driven by the preponderance of the Type 1 events, as I mentioned before.

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To assist the robustness of the Clozaril treatment effect, a Cox Proportional Hazard Analysis was carried out for each of several diagnostic and demographic subgroups, so that's for the schizophrenia and schizoaffective diagnostic subgroups, treatment-resistant and treatment-nonresistant, look at geographic distinctions for North America and the rest of the world -- gender, race and age grouping.

For the subgroup, the hazard ratio was less than 1, confirming the reduction in risk in the Clozaril group relative to the Zyprexa group for a suicide attempt or hospitalization to prevent suicide. Remember, less than 1 is in favor of Clozaril.

Also note that the hazard ratio of the individual subgroups are very close together, thus demonstrating a high degree of internal consistency.

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Now I'd like to review the changes in the secondary clinical assessments which were carried out during InterSePT.

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Looking first at the change from baseline in the severity of suicidality as rated by the blinded psychiatrists on the CGI-SS-BP, you see that they were

equal or very similar proportions of patients form the treatment groups, each change category at the end of study, that explains a bit -- these are the change categories, so the CGI-SS-BP is a change from baseline scale. So, relative to baseline, in this case, about 25 percent of the patients in each group were rated very much improved; about 30 percent of the patients in each group had no change relative to baseline; about 5 percent of the patients overall in each group had some degree of worsening in suicidal status, as rated by the blinded psychiatrist at the site.

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Here are the other secondary measures. You see for the ISST-BP, much the same result as for the CGI-SS-BP. Relative to baseline in both treatment groups, there's a reduction in the score from the baseline of 7.4 by about 5 points at the end of the study. This considerable reduction is essentially the same in both treatment groups. This pattern of response also holds true for the psychopathology variables. On the PANSS-T, CDS and Covi, there are very similar reductions in the groups relative to baseline, and these are mostly indistinguishable.

Here are some of the results we've seen sos far. For Clozaril patients relative to Zyprexa

patients, there was a significant reduction in the risk of experiencing suicidal behavior, Type 1 or Type 2 event. However, from the results we see here this difference appears not to be related to differential improvement in measures of psychopathology or measures of suicidality as rated by the blinded psychiatrist.

There are perhaps a number of reasons for this finding. One might be the fact that the assessments of psychopathology, especially the CGI-SS-BP and the ISST-BP, occurred at only a few discrete time points separated by intervals of eight weeks, while the patient's suicidal behavior is obviously not tied to these time points. Thus, these assessments ultimately may not contribute to the assessment of drug effects.

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There was an intrinsic of Clozaril on suicidal behavior. I don't want to speculate on this now, but if that is the case, it would be important to address the possibility that such a drug effect may be confounded by the greater use of concomitant psychotropic medication in the Clozaril group. Remember, there was no constraint on the use of psychotropic medications.

To look at this possibility, or to examine

this possibility, we looked at the use of concomitant psychotropic medication in the two groups during the study. Specifically, the concomitant psychotropic medications in the four classes -- antipsychotics, antidepressants, sedatives/anxiolytics, and mood stabilizers, we used equivalents to get these drugs into a common denominator -- Haloperidol equivalents for antipsychotics; fluoxetine equivalents for antidepressants; diazepam equivalents for sedatives/anxiolytics; and carbomazepine equivalents for mood stabilizers. For each of the four classes, as we see here, there's a significant difference between the groups with respect to the mean dose of these classes of medication. In each case, the mean dose of each of these medication classes is significantly greater in the Zyprexa group. This result would appear to discount the possibility that the effect of Clozaril on the risk of suicidal behavior is due to a greater use of adjunct psychotropic medication.

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To move on to discuss the safety aspects of the study.

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As could be expected in a two-year study,

90 percent of the patients in each group had at least one adverse event report. About half of the patients in each group also had at least one report serious adverse event. However, there were no cases of agranulocytosis, myocarditis or cardiomyopathy in the Clozaril group. There was 1 case of cardiomyopathy in the Zyprexa group.

On the following slides, I will present the adverse events of interest for Clozaril adverse events separately, then consider the psychiatric and neurologic adverse events and deaths for the two groups together.

(Slide)

Looking at the Clozaril adverse events of interest, we see that the incidence of salivary hypersecretion, white blood cell decrease, constipation, weakness, postural hypertension, and convulsions is greater in the Clozaril than the Zyprexa group.

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On the other hand, looking at the Zyprexa adverse events of interest -- weight increase, dry mouth, asthma, laceration, epistaxis -- are greater in the Zyprexa group. The incidence of diabetes mellitus NOS, not otherwise specified, is about the same in the

two groups. The reports of laceration we see here were not related to suicidal intent.

(Slide)

This slide summarizes the frequencies of psychiatric and neurologic adverse events in the two groups. The blue field are those events where the occurrence or the frequencies of events are higher in the Zyprexa group -- that's depression, suicide ideation, suicide attempt -- again, as adverse event reports -- drug abuse, tension, mood disorder, insomnia, akathisia are greater in the Zyprexa. In the yellow text area, we see that somnolence, dizziness, dysarthria and syncope are greater in the Clozaril group.

(Slide)

There were 22 deaths during the study, of which 10 were suicides. During the two-year observation period, there were 5 suicides in the Clozaril and 3 in the Zyprexa group. In each group there was 1 suicide -- that's the number in parentheses -- that occurred after the two-year observation period, but within the 30-day safety followup period. Considering the high-risk population of InterSePT, the number of suicides was very low. The difference in the number of suicides attributed to

the groups is not statistically significant.

The other deaths that occurred during the study were associated mostly with cardiovascular or oncologic events. With regard to the single fatal motor vehicle accident we see, there was no evidence to indicate that this was the result of suicidal intent.

(Slide)

In the final part of my presentation, I'll address one of the questions raised by the FDA during their review of InterSePT results. This question concerns the process of referring case material from the unblinded Principal Investigator to the blinded Suicide Monitoring Board.

(Slide)

Now, the situation involved in this question is perhaps best explained if we take another look at the flow chart describing the movement of unblinded data to the blinded Suicide Monitoring Board, as I mentioned before. The information was collected at the site by the Principal Investigator, information concerning potential Type 1 events, potential suicide events or hospitalization to prevent suicide. This information was collected in a nonblinded fashion. The Principal Investigator was

aware of all the assessments going on, was in many cases the actual treating physician for the patient. This information was passed on to the Medical Monitor who blinded it and passed it on to the SMB.

Because the PI is aware of the patient's treatment, there is obvious potential bias here. During the study itself there were a number of checks in place to identify potential Type 1 events that may have been missed by the PI. In particular, the Medical Monitor reviewed adverse event and serious adverse event reports; all hospitalizations, medical and psychiatric; and reports of self-harm, and actually anything vaguely associated with self-harm.

If there was any evidence in this body of data to indicate that the PI may have missed a potential Type 1 event, the Medical Monitor contacted the site and queried the investigator. At the same time this was going on, on a regular basis the field monitors reviewed the source documents for all unreported cases of suicidal events, and in those cases where there was no referral to the SMB, they made sure that there was no evidence there for potential Type 1 event.

In response to the FDA's recent request, Novartis conducted a retrospective review of the

referral process, which I will now describe.

In our review of the process of referring Type 1 events from the Principal Investigator to the SMB -- potential Type 1 events, excuse me -- we made the assumption to refer the bias when we ruled the case not referred to the SMB. Nonreferral of potential Type 1 information occurred in 701 of the 980 patients who were enrolled in InterSePT. The search term dictionary or glossary, to use the technical term, were then developed, which was based on terms from the reports clearly corresponds between the investigative sites, the Medical Monitor and the Monitors, in comments from the site staff entered into the case report forms which comprise the documentation for each case.

There were more than 300 terms in the search dictionary, covering not only explicit suicidal behavior, but also events not necessarily related to suicidal behavior, such as drunkenness or abrasion.

The next step in the search term dictionary was applying to each of the 701 cases, looking for matches -- the search dictionary was programmed to look for matches in each of the 701 cases. The search program was blinded to patient treatment.

The case report forms from those cases where terms were matched were then reviewed by Novartis. For example, if the term "abrasion" which was in the search dictionary, popped anywhere in a patient's case report form, the entire documentation from that patient was then reviewed by Novartis clinical staff. The review covered several -- well, three questions were asked: Whether the term was potentially related to suicidal behavior or was related to potential suicidal behavior? If so, were the PI queried regarding occurrence of suicidal behavior? And if the PI was queried, what was his or her response? We then graded this review to establish whether potential cases of suicidal behavior were not referred to the SMB for a blinded and independent assessment.

(Slide)

Now, the results of our review, so summarized here. There were matches of at least one dictionary in 279 out of the 701 cases -- that is, again, the 701 cases represent those patients for whom no there was no potential Type 1 event which had been referred prior to the SMB. In 279 of the 701 cases, there was at least one search-term match -- again,

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these cases were we able to determine that there was evidence indicating that there may have been a Type 1 event, evidence for potential Type 1 events here.

We feel that the results of this review that, although the Investigators were unblinded to patient data, they acted without bias in referring case material to the SMB.

(Slide)

To move now on to conclusions from InterSePT. During InterSePT, treatment with Clozaril compared with Zyprexa was associated with a 26 percent reduction of risk for a suicide attempt or a hospitalization to prevent suicide.

For all subgroups examined, there was a high degree of consistency in the reduction of risk for suicidal behavior in the Clozaril group compared to the Zyprexa group.

(Slide)

The reduction in risk in the Clozaril group appears not to be attributable to a greater effect on psychotic or depressive symptoms, or to a greater use of concomitant psychotropic medications. Adverse event profiles for both study drugs were generally consistent with previous experience and current product labeling. Finally, the open-label

design was not associated with biased assessments by the Principal Investigators.

(Slide)

The overall conclusion, the results of InterSePT show that Clozaril is effective and safe in reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are at risk for suicide.

I'd like to introduce Dr. Kane, who will present the risk/benefit assessment for Clozaril in the treatment for reducing the risk for suicidal behavior.

DR. KANE: Thanks very much. I'm very pleased to have been part of this project which I think is important not only because of the significance of the results, but also because it demonstrates that studies can be conducted in high-risk populations in a way that is both safe and scientifically informative, as well as clinically meaningful.

(Slide)

As clinicians, we need to assess the benefit and risks of treatment interventions. When considering the benefits and risks regarding the use of Clozaril in the treatment of suicidal behavior, one

needs to consider both the risks of treatment intervention and the benefits of reducing suicidal behavior. But in this assessment, one must also consider the risk of not treating these patients.

(Slide)

As you know, Clozaril was first approved in 1969 for the treatment of schizophrenia. After 33 years of use, it is recognized as the most effective agent in the management of treatment-resistant and partially-responsive patients. Despite numerous efforts, no other second-generation drug has been able to match Clozaril's consistent efficacy in this population.

In addition, over the years, other properties and clinical uses of Clozaril have drawn increasing interest and attention. Some of these include reduction in substance abuse, smoking, movement disorders, aggression and violence and, importantly, suicidal behavior.

Many of these observations came from uncontrolled or small trials or epidemiologic studies. The pivotal study that we're discussing today obviously represents an extremely well-designed and well-controlled trial attempting to look at the issue of suicidal behavior.

(Slide)

The burden of suicidal behavior is very clear. Left untreated, it's associated with increases in morbidity and mortality; hospitalizations both psychiatric and medical; emergency room visits; interventions to prevent suicide attempts such as the use of concomitant medications and increased surveillance. The family burden is enormous, and anyone who has worked with families in this context can appreciate the tremendous strain and sense of anxiety that this creates. The societal costs, as you heard earlier today, are also substantial.

(Slide)

Well, the InterSePT study clearly provides a new basis for understanding potential benefits and potential risks of Clozaril utilization. It was a well-designed study that was consistent, with very valuable input from the Food and Drug Administration. It utilized prospectively defined and objectively rated endpoints that were assessed by, as you've heard, a blinded Suicide Monitoring Board.

The study compared two atypical antipsychotics over a period of two years, which allowed for a long-term perspective on the efficacy and safety outcomes. Very importantly, procedures

were designed to maximize patient safety and, as we've seen, the overall rate of completed suicides in this study was remarkably low.

(Slide)

Now, as you've seen in Dr. Zaninelli's presentation, there were a number of statistical methods brought to bear in the analyses. Clearly, from my perspective, the most impressive thing is that there was consistency across a variety of ways of looking at this, demonstrating the superiority of Clozaril in this high-risk population.

Now, these two analyses demonstrate the statistical superiority of Clozaril over Zyprexa in reducing suicide attempts or hospitalizations to prevent suicide.

(Slide)

Here, we're looking at the Kaplan-Meier estimates of the cumulative probabilities of suicide attempts or hospitalizations to prevent suicides. Again, this analysis demonstrates significant superiority for Clozaril over Zyprexa.

(Slide)

Now, the previous slides involve the key statistical comparisons. From a clinical standpoint, it's also very impressive to see the consistency of

clinically meaningful differences across measures of suicide attempts and hospitalizations, and we see that on the left-hand side of the slide.

It's also important to note, these are items you saw in Dr. Zaninelli's presentation from the adverse events reports, and I think from a clinical perspective it's very valuable to look at the adverse event reports as another source of information. When clinicians are treating patients, they are not usually filling out rating scales, but they are responding to reports from the patient of what might be considered adverse events.

Here we see that depression as an adverse event occurred significantly more frequently in the Zyprexa-treated patients. Suicidal ideation reported as an adverse event also significantly more frequent in the Zyprexa-treated patients. So, this, I think, just is another way of getting a sort of clinical sense of how these differences emerged and how many different ways.

(Slide)

In addition, these differences were apparent despite the fact that as you saw previously, Clozaril-treated patients received significantly less concomitant medication in ever psychotropic drug

category. Dr. Zaninelli had presented the mean daily dose of concomitant psychotropic medication, and shown significant differences in each drug category. Here, we're looking at mean daily dose displayed over time for each category of adjunctive medication -- antipsychotic, sedative/anxiolytic, antidepressant, and mood stabilizer.

So, the superiority of Clozaril in the array of measures that have been discussed was apparent despite the fact that the Zyprexa-treated patients received consistently more adjunctive medication.

(Slide)

Well, to place the current use of Clozaril in the context of the benefit-to-risk ratio, it's important to consider where we are in our understanding and management of some of the serious adverse effects that can occur with Clozaril, the first being agranulocytosis. The current estimated incidence in the U.S. is 0.3 percent during the first year of treatment, and then it goes down considerably after that. There is clearly a well-established risk management system which has contributed to the very low levels of morbidity and mortality currently associated with agranulocytosis.

More recent concern has arisen around the risk of myocarditis. The current incidence in the U.S. is estimated to be 5 per 100,000 patient-years.

Seizures or convulsions are another adverse effect that is associated with Clozaril, and the current incidence estimates in the U.S. package insert is 3 percent.

Weight gain and disturbances in glucose regulation are also adverse effects associated with Clozaril and some other second-generation antipsychotic drugs.

(Slide)

The averse events associated with Clozaril in InterSePT were generally consistent with previous clinical experience. There were, in fact, no cases of agranulocytosis, myocarditis, or cardiomyopathy in the patients treated with Clozaril. Convulsions occurred in 2.5 percent of patients, that's 12 individuals out of 479 patients, and that's very consistent with prior experience as well as the package labeling.

(Slide)

So, Clozaril proved to be superior to Zyprexa in reducing both the overall number of suicide attempts and the overall number of hospitalizations to prevent suicide. What we see, in fact, is a very

impressive 26 percent reduction in the risk of suicide attempts or hospitalizations to prevent suicide for Clozaril relative to Zyprexa. And, of course, this has tremendous implications. This clearly leads to the potential for lower health care costs through a reduction in hospitalizations and less frequent use of concomitant psychotropic medication, as well as decreased surveillance necessary to attempt to prevent suicide.

(Slide)

Well, to really put this in perspective, let's translate the InterSePT data into the so-called number needed to treat analysis. So, when we do this, Clozaril has a two-year number needed to treat of 13 patients. Now, what does this mean?

If 13 at-risk patients were treated with Clozaril instead of Zyprexa, we would prevent 1 suicide attempt or 1 hospitalization to prevent suicide.

(Slide)

Now, fundamentally, as clinicians, we need to assess the benefits and risks of treating patients, as well as the risks of not treating patients. When assessing the benefits and risks of using Clozaril to treat suicidal behavior, we need to look at the most

significant risks, agranulocytosis and myocarditis, versus the benefits, and that is the reduction in suicide attempts or hospitalizations to prevent suicide.

Here, we see that based on our current estimates for agranulocytosis and myocarditis, that for every 1,000 patients treated for two years, approximately 3.5 would experience agranulocytosis, fewer than 1 would experience myocarditis. This compares with a dramatic reduction in suicidal behavior with Clozaril treatment because we find that for the same 1,000 patients treated for two years, 77 would be prevented from a suicide attempt or hospitalization to prevent suicide.

(Slide)

As we've heard, suicidal behavior in patients with schizophrenia or schizoaffective disorder is a serious public health problem and represents an important unmet medical need. The analysis of the safety and efficacy results from InterSePT taken together with the published literature demonstrate that the beneficial effect of Clozaril in reducing suicidal behavior clearly outweighs the associated risks.

These data are very impressive and

clinically valuable. I believe that they should serve as the basis to extend the indication for Clozaril. As always clinical judgment is critical in deciding for which patients to recommend this treatment, but I would emphasize how important it is to give our patients and their physicians this option. Thanks very much.

DR. OREN: At this point, I'd like to invite members of the committee with questions for the Novartis to offer them.

DR. ZANINELLI: I will be the moderator for Q and A here.

DR. OREN: Dr. Winoker.

DR. WINOKER: I've got a few questions, should I just run through those?

DR. OREN: Sure.

DR. WINOKER: The first is, with respect to the dosing guidelines that you've mentioned, you also mentioned that 18 percent of the patients on olanzapine were at doses above the recommended upper dose. So, I was just interested in whether the recommendations were just recommendations but Investigators were perfectly free to use their judgment, or they were really expected to stay within the 5 to 20 -- and this actually represented people

going outside of what you had intended with the study design.

DR. ZANINELLI: Right. As I tried to make clear, the dose recommendations were in line with the prescribing information occurring at that time, 1997. Most of the clinicians in the audience will know the Zyprexa tends to be dosed outside, above that recommended range. But as the sponsor of the study, we were not able to go outside the labeling, so to speak. But it was to be expected that for both groups, actually, there would be dosing outside the range. It just happened more in the Zyprexa group.

DR. WINOKER: As it turned out, the dosing range for olanzapine actually conformed to current practice and that's very nice, but I guess what I'm trying to clarify is this would not have been considered a violation of the expectations of the study in terms of Investigators not following specific instructions.

DR. ZANINELLI: Not at all, it was not a protocol violation.

DR. WINOKER: And I had a second question about the use of adjunctive medications, particularly the antipsychotics. You did a very nice job of summarizing how that broke out across the different

categories.

We saw in one of the information packets that we got that there were a few instances of patients assigned in the protocol to Clozaril, who ended up receiving olanzapine as well, and conversely. That appeared to be a limited number, but I just wanted to understand how that might have affected data analysis and if you did any further assessments to make sure that there weren't -- that clearly could have represented -- confounded interpretations.

DR. ZANINELLI: Right, that's true. Because, as I tried to explain, in the study design there were no constraints on the use of concomitant psychotropic medications, including using the other study drug to treat patients who were assigned to Clozaril or Zyprexa.

(Slide)

And as you see here in this summary, 69 patients who were assigned to Clozaril received olanzapine at some point during the study. This could have been during the transition phase where they're coming off olanzapine and coming on to Zyprexa, but there was possibly a period in individual cases where they were getting both drugs. And 17 Zyprexa patients also had clozapine as a concomitant medication.

Again, it could part of the function of the transition phase.

If we exclude these patients from the analysis, the results of the WLW analysis actually are a little bit more robust, at .021.

DR. WINOKER: Thank you. The next question I had is, there were four initial inclusion criteria for identifying high-risk individuals, and I wondered if you conducted any type of analysis -- I'm sure you did, so if you could share a little bit of that with us in terms of how subjects distributed across the two treatment groups in terms of representation for one or more than one of the criteria. I'm asking that because two of them represented historical information that could have gone back up to three years, and the other two were more -- you know, very current -- within the past week.

DR. ZANINELLI: Right. We do have the one slide showing the number of events across the two groups. So, we showed you the mean, but we could actually break that down to 1 to more than 5 events. Could we get that information? Maybe John Kane could answer to that as well.

While we're pulling up some relevant data,

I think it would be important to point out that about 80 percent of the patients participating had at least 1 hospitalization or 1 suicide attempt, as a qualification for the study. So, the overwhelming majority met those two criteria.

(Slide)

DR. ZANINELLI: No, this is not what I meant. At baseline, the distribution of suicide attempt and hospitalization to prevent suicides by the categories 1, 2, 3, greater than 3 -- I don't know if you have that or not.

In any case, we look at the past history of suicide behavior, drilling down into the numbers, they are essentially the same for both treatment groups. So, although the mean of greater than 3 in each group, there were no more patients having greater than 5 in the Zyprexa or Clozaril groups than the other group. Here, this is the one.

(Slide)

So, just looking at lifetime attempts, again, the number of patients who had no attempts was relatively low, and then we broke it down to 1, 2 to 3, 4 to 5, and greater than 5. And, again, we see that regarding the past history, there were similar numbers of patients in both groups having 1 or

specific numbers of events. This is also true for hospitalizations.

DR. WINOKER: Thank you. And the last question I had, in discussing the issue of referrals of the Type 1 events to the Suicide Monitoring Board, what type of training or instruction were provided to the Investigators at the different sites in terms of how to approach identifying what rose to a level of the case that should be brought forth?

DR. ZANINELLI: Okay. In general, the information had to be collected in a potential endpoint package, which consisted of a series of forms. I think Dr. Kevin Cox is here, he could perhaps prescribe the -- he was the Medical Monitor for the U.S. -- perhaps describe what sort of information, or how the PIs were prepped, and what sort of information was in the potential endpoint package.

DR. COX: I'm Kevin Cox, from Inginex Pharmaceutical Services. I was the Medical Monitor for North America. At the Investigator meeting, Investigators were told that we wanted to look at any event that was related to suicide, that included a hospitalization or a potential attempt.

The packet that was included -- I think

Dr. Krishnan pointed out -- there was a suicide attempt form for any patient who had a potential attempt. There was an imminent risk of suicide requiring hospitalization form, which included all the reasons why they felt that hospitalization was related to suicide. There was some of the scales, the InterSePT scale for suicidal thinking, the Calgary scale, and then there was the hospital reports.

DR. ZANINELLI: I hope that answers the question.

DR. WINOKER: Thank you.

DR. OREN: Dr. Rudorfer.

DR. RUDORFER: We were told about the visit schedule in terms of the weekly for six months and then biweekly. Were those the clinical visits as well as the --

DR. ZANINELLI: Not necessarily, no. For instance, you mean the assessment visits for CGI-SS-BP and ISST?

DR. RUDORFER: Yes.

DR. ZANINELLI: No, they were not. Those were at eight-week intervals, actually. There was a baseline, I think, at week 4, and after that at eight-week intervals. So those did not correspond with the clinical assessments. However, they did correspond

with assessments of adverse events, or if an adverse event report came in during that one-week interval or two-week intervals, they went into the database. Dr. Kane spoke to that. So, actually, there were more assessments than adverse events regarding suicidality than there were assessments of suicidality status.

DR. RUDORFER: If I could return to the concomitant medication issue for a moment, Dr. Meltzer, before, presented his 1995 study with clozapine monotherapy, and I wonder if there are data in the InterSePT study in terms of clozapine monotherapy versus olanzapine monotherapy, at least in terms of antipsychotic monotherapy.

DR. ZANINELLI: So the question is were there patients who had only Clozaril or only Zyprexa alone?

DR. RUDORFER: Yes.

DR. ZANINELLI: To my knowledge, during the whole course of the study, there was no patient who was on either study drug for any length of time, solely on that study drug without a concomitant medication.

DR. RUDORFER: Okay. How about where the concomitant medication were only non-antipsychotics?

DR. ZANINELLI: Do we have the

availability of information due to patients taking study drug plus just one class of medication with -- I don't think we have that analysis up to now, no. It was actually very few patients who would not take -- the mean number of drugs was about three for the Zyprexa group and 2.5 on the Clozaril group. So there were very few patients who were not taking at least one or two concomitant medications at any point in the study.

DR. RUDORFER: I still have the floor. Can I ask another question?

DR. OREN: Yes.

DR. RUDORFER: I want to go back to the issue of diagnosis. We've heard DSM4. How were the data gathered? Was there a structured interview, or how was the diagnosis made?

DR. ZANINELLI: The SCHD (phonetic) or mini-SCHD (phonetic) were not carried out, so there was no documented structured interview, but the protocol did stipulate the application of DSM4 criteria for these two diagnoses.

DR. RUDORFER: Now, DSM4 indicates that a type of schizoaffective disorder should be specified, either bipolar or depressive. And I wonder if that information was gathered?

DR. ZANINELLI: I don't think -- that was not gathered, no. That was not gathered. That was only schizoaffective disorder, present or not.

DR. RUDORFER: Okay. May I refer to a case in our material? A patient report that I noted, a patient in the Zyprexa group received a diagnosis called "schizomanic relapse" -- I can refer to the exact case, but I wondered what that --

DR. ZANINELLI: I assume that's a European case. Dr. Krishnan perhaps can give the details on that.

DR. KRISHNAN: Just to briefly address this, I think it's very clear that a diagnosis of schizoaffective probably depends on which country we were getting the patients from, and it probably again reflects the fact that that diagnosis is a hard one to make even under the best of circumstances. So while we use the term "schizophrenia/schizoaffective", it's more important to think of this as people who have psychotic behavior looking like schizophrenia, which is consistent, in addition to some degree of affective disorder. And if you look at the case, it's not the CRFs but the way people write notes, and you get translations of the notes which was done, you would find people with all sorts of different additional

labels, probably reflecting the country of origin.

DR. RUDORFER: My concern is that -- and my understanding the reason why DSM4 calls for the subtype differentiation is that there may be differences in the clinical course of the subtypes, that the bipolar subtype may look more like mood disorder as opposed to more like schizophrenia. So I was concerned that a patient called "schizomania" might be closer to a mood disorder patient.

DR. KRISHNAN: you read the notes, most of them are schizophrenia with or without significant affective disorder, and having had a chance to look through the history of at least the people who came into this, these are not bipolar patients, these were patients you would -- when you try to label them, schizophrenia remains like the core context, and then on top of it you have drug abuse, alcohol abuse, everything you name. This is the patients you can use a lot of labels, that's important to keep in mind. You see them in the emergency rooms. This is the kind of patient, you do an interview, and if you go through a checklist, you can add on additional labels with the core construct of schizophrenia.

DR. RUDORFER: Thank you.

DR. MELTZER: I think there are some data

which speak to having more confidence in the differentiation between the two groups, namely, that if you look on the history of number of hospitalizations for suicide and number of suicide attempts, the group diagnosed as schizoaffective had significantly more than the group diagnosed as schizophrenia. Then during the study, the group diagnosis schizoaffective disorder went on to have more Type 1 and 2 events of more severity, and that is consistent with the literature for schizoaffective disorder. Had it been just sort of a random term applied, I don't think you would have seen that.

DR. OREN: Just to follow up on that specific point, there was one bit of data presented, I think in your Slide 39, showing the relative efficacy of Clozaril versus olanzapine for schizoaffective disorder. That particular subgroup was perhaps the least impressive of all the different subgroups on that slide. Do you have any additional data teasing out the difference between responses between the schizoaffective and schizophrenic groups?

DR. ZANINELLI: Do we have --

(Slide)

Following from that last slide -- the number of percent of Type 1 and Type 2 events by the

diagnosis subgroup -- so, schizophrenia, schizoaffective disorder for Clozaril and Zyprexa -- we see here the ends for the respective diagnoses and the Kaplan-Meier estimates. So, for both diagnoses, in the Clozaril group, the probability of having a Type 1 or Type 2 event is less than it is in the Zyprexa group. It's somewhat higher in the schizoaffective group, but it's still comparable.

DR. OREN: Dr. Ortiz?

DR. ORTIZ: I would be interested in hearing a little bit more and some elaboration on why a structured interview was not used.

DR. ZANINELLI: Dr. Meltzer will probably be best because he was one of the designers of the study.

DR. MELTZER: There was considerable discussion and desire to do that. It was felt that the three hours or so that it would take to do it, given the context of the study, was not something that various of the sites were prepared to do.

DR. OREN: Dr. Katz.

DR. KATZ: I have a few questions -- four, actually. The visits, as you say, were between four and eight weeks apart, although I know they were seen more frequently for blood draws or vital signs. What

was the procedure for ensuring that all events of interest were actually captured? For example, it might have been possible the patient would have been hospitalized for a suicide attempt at some distant hospital not related to the study site. What exactly were the PIs instructed to look for or ask for in that sense?

DR. ZANINELLI: That -- and, again, it's accurate to say that many of these hospitalizations occurred in the interval and not necessarily at the site where the patient was being treated during the study, but the information did flow into the adverse event and serious adverse event forms, and that was the main source of information.

DR. KATZ: What I'm asking is what was the process by which you ensured that that happened? How was that that information from a distant site flowed, as you say, to the adverse event forms?

DR. ZANINELLI: Perhaps Kevin again, the Medical Monitor for the study.

DR. COX: At each visit, patients were asked how they were doing, has anything happened since their last visit. So, it was pretty much reliant on patient report. In addition, sites were instructed to gather information from collaborative sources wherever

they could.

DR. KATZ: Maybe just one other question, and I have several I could ask later. There were a number of, as you call them, "retrieved dropouts". Could you possibly present some data on the events, Type 1 and Type 2 events, that occurred during that period of time after the patients were discontinued from study group?

DR. ZANINELLI: Okay. We have a number of analyses looking at retrieved dropouts.

(Slide)

Okay. Again, the definition of "retrieved dropout". Again, a stipulation of the study protocol was that if a patient discontinued the study before the end of their personal two-year observation period, every attempt should have been made to follow-up that patient at least with respect to the occurrence of a Type 1 or Type 2 event.

So, how many patients were there that were retrieved dropouts? There were about 60 in each group. And this looks at of those patients, about two-thirds of them, 60 percent, had no Type 1 event after dropout, and about 30 to 40 percent had a Type 1 event. So, this was a useful method of accruing data to the analysis of the primary endpoint. Again,

it was not possible in all cases to get this information. Patients were lost to followup or changed clinics or whatever.

DR. OREN: Dr. Hamer.

DR. HAMER: I have a possibly related question. For the survival analyses, for a Type 1 event, did you actually capture data to the actual day that it occurred, or was it rounded to the week of the nearest visit or something like that?

DR. ZANINELLI: It was actual date.

DR. HAMER: What about Type 2 events?

DR. ZANINELLI: Also --

DR. HAMER: I mean, I understand that most of the Type 2 events were actually Type 1 events, but some of them were reports of increased suicidal ideation, and I wonder how you would capture those to the days on which they actually occurred.

DR. ZANINELLI: Okay. Dr. Zahur Islam is the Chief Statistician for the project, and probably can give the best information on that.

DR. ISLAM: A Type 2 event is a combination of Type 1 and worsening of CGI-SS-BP to a scale of 5 and 6. CGI-SS is measured at the scheduled visit, so part of the Type 2 events were from the scheduled visit, and it affected, as you have seen, on

the 18 and 20 patients there.

DR. OREN: Dr. Katz.

DR. KATZ: Just a followup. Could you put that slide back again, is that possible? The last one you showed about the Type 1 and Type 2 events.

DR. ZANINELLI: The retrieved dropout slide, the last one we showed?

DR. KATZ: Yes. I just want to make sure that I understand what it showed.

(Slide)

This is the number of -- there's a footnote at the bottom that says "12 Clozaril and 3 Zyprexa patients had Type 1 events after discontinuation". How does that jibe with the numbers that you have up on the chart? Maybe I'm just not understanding it. The second row on the chart seems to say that there were 20 Clozaril patients who had a Type 1 event.

DR. ZANINELLI: Right. Is that before discontinuation?

DR. KATZ: What I'm interested in is what happened during the retrieved dropout period.

DR. ZANINELLI: Jay Shu would be best able to answer that.

DR. SHU: Jay Shu, statistician for

Novartis. The 20 and 25 patients with Type 1 events, the 12 is actually out of that 20. Twelve patients that had an event after discontinuation.

DR. KATZ: And only after discontinuation, is that right?

DR. ZANINELLI: Right. So that was my mistake. Then these are the patients who had Type 1 events overall, and of those, 12 were after discontinuation in Clozaril and 1 in Zyprexa.

DR. KATZ: And that -- the 12 and the 3, that was the first time that they had a Type 1 event because, obviously, patients could have more than one Type 1 event.

DR. ZANINELLI: In all cases were first Type 1 events, yes.

DR. OREN: Dr. Wang.

DR. WANG: As long as we're dealing with analyses, in terms of the WLW approach, it certainly advantageous to use it. One of the assumptions, though, is that it's ideal for current events, true distinct events, and I was wondering if you could comment on the fact that some of these might be remeasures of the same event -- in other words, if someone has a decline in their score as well as has a Type 1 event, that could be the same thing.

DR. ZANINELLI: Right. Dr. Lin, would you like to comment on that?

DR. LIN: Hi. Danyu Lin, from University of North Carolina. The WLW method can be used to analyze various type of multivariable data. You could have a multiple event per person, and a multiple event could be the recurrence of the same of event, or it could be distinct events. And the correlation usually among different events, especially if you consider a distinct event.

In our case, the Type 2 event includes a Type 1 event. So, they obviously had to correlate it. And, statistically, actually, this is -- it's very simple. All we are doing is basically we fit two standard per person who had this model to each of two events, so I had the original estimates for the time of the first event and hazard ratio estimate for the time of second event which, in this case, are very similar -- .76 and .74. All we do is that we combine the two estimates. We just take an average of the two estimates. And because we take an average of two estimates for two highly correlated data, we know the correlation, but statistically that's what the method is for, it's to estimate the correlation empirically from the data, and correlate it just for the

variation. And so the correct variance is used in the denominator, and in the numerator you basically just average out the two estimates, and it give you just a normal statistic.

DR. WANG: Could I follow that up with another related question, and that is why you see a lack of efficacy when you look just at the blinded psychiatrist ratings -- you know, if you look at your hazard ratios, if you just do an analysis on Type 1 events, you have a ratio of .74. When you add in the Type 2 events, which the only new contribution is via the blinded psychiatrist ratings, the hazard ratio, if anything, gets a little bit worse, to .76.

DR. LIN: Can we show that slide? Can we show the number of events, the definition -- the one that we showed when we show the results of the study, when you show the composition of the Type 2 event.

(Slide)

Basically, it is that the difference between the two groups is most substantial in Type 1 event than the additional number of Type 2 events that's not a Type 1 event.

DR. WANG: The additional, when you add in the blinded psychiatrist ratings, it's not that it only adds a little, it actually detracts from the

benefit seen with Type 1.

DR. LIN: No, I'm talking about 18 out of 20, that difference is very small. Maybe I misunderstood your question.

DR. WANG: If you look at the regression co-efficient just for the psychiatrist ratings, it's actually in favor -- slightly in favor, and it's highly nonsignificant, but in favor of Zyprexa. I'm interested in your thoughts on why that might happen.

DR. ISLAM: As you can see, the Type 1 event separation, 102 and 141 patients. The Type 2, the CGI-SS contributed 18 and 20 to the Type 2. If you compare the 18 and 20, it's not much of a difference.

Now can I see Slide 37, please.

(Slide)

That's what it looks like in here because the CGI-SS didn't contribute much. So the co-efficient includes little, and that is the reason here.

DR. WANG: Any thoughts on why it didn't contribute? I mean, any thoughts on why the psychiatrist ratings had not contribution?

DR. KRISHNAN: Let me just briefly address that. I think it's really a question of how often were the ratings obtained, which were much more spread

out -- 4 weeks, 8 weeks, up to 12 weeks in the second part of the study. And the second reason for that is we actually looked at how these events happened, what type of precipitations of suicide. They actually don't correlate so much to the scaling that is done in the event-by-event thing. It probably correlates just to the time point closest to it. So, if you came in a week before and they did the scale, that correlates pretty well. But if you had come in 8 weeks before, it may not because the events seem to be more related to what's happening in the life of the individual leading to that particular trigger. And those scales do not capture the trigger factor.

So, although I think it was a nice addition, I don't think it actually added much value to the overall thing, and there are two reasons -- one, the frequency and, second, they were not time-relevant to the events because the events were different periodicity, if you want to call it, not connected to in the scale.

DR. OREN: Dr. Katz.

DR. KATZ: I have two questions related to the blind. There were various attempts, as you described them, to address the question of potential bias by the unblinded psychiatrists referring cases.

As I understand it,the Inginex staff could also refer cases, and presumably, of course, the Medical Monitor could identify cases that would be assessed in a blinded way by the Suicide Monitoring Board, but I'm just wondering what aspect of that -- the staff's, Inginex staff's referral or identification of additional cases was blinded. Was any of it blinded, or was that also unblinded?

DR. ZANINELLI: Inginex was not -- the Medical Monitor was not blinded, just performed the blinding.

DR. KATZ: Right, but it was also the Medical Monitor who could decide that there might be additional cases that could be sent to the SMB for blinded review, is that right?

DR. ZANINELLI: The Medical Monitor would essentially challenge the Principal Investigator if he found evidence for a potential Type 1 event, but it was ultimately the Principal Investigator who referred the case. It was blinded by the Inginex Monitor.

DR. KATZ: So there were no cases that the unblinded Medical Monitor for Inginex could identify independent of the cases identified by the unblinded investigator, they couldn't independently identify a potential case and then ship the blinded data to --

DR. ZANINELLI: They could because they were independent of the referrals reviewing in real-time, so to speak, the adverse event.

DR. KATZ: Right, that's my point, but they were doing that in an unblinded way as well, is that correct?

DR. ZANINELLI: Yes, unblinded.

DR. KATZ: That's really just the point I want to make. The other had to do with your attempt to go back and look at the 700 unreferred patients and identify cases. You described in some detail the steps that were taken to identify any additional cases, and somewhere along the line you said a particular step was blinded. I'm wondering if you could speak more explicitly about how you decided that some cases might have actually been Type 1 events. Was it basically an unblinded look at the case report forms and that sort of thing?

DR. ZANINELLI: Right. The program that was doing the match was unblinded to treatment. Ultimately, the Novartis staff -- there's a time issue here as well -- were not blinded necessarily, they could look into it if they wanted to. And we used the same criteria. Again, anything that -- any bit of evidence that was -- could be a potential Type 1 event

was considered.

DR. KATZ: Right, but those events were identified in an unblinded way, presumably. And then when you actually went and got those cases that were potentially Type 1 events, the review of that material was also unblinded.

DR. ZANINELLI: Was unblinded, yes.

DR. LAUGHREN: Just again a clarification. The material that was available to the Novartis reviewers in looking at the data from these roughly 300 cases that matched on adverse event terms, as I understood it, that's information only that was in the case report forms.

DR. ZANINELLI: The case report forms and -- James -- James Rawls, from Regulatory Affairs, who supervised the review.

MR. RAWLS: Good morning. James Rawls, from Regulatory Affairs. I helped to assist with the team that reviewed these events. There was a variety of information -- the same information that the SMB reviewed we had available, with the exception of the clinical history, but I think it should be pointed out that the majority of those events, since we picked up every term that could have been a suicide attempt or something related to suicide, the majority of those

that related to suicide attempts occurred prior to randomization. They were dealing with a baseline history information, and not events after randomization.

And then if you looked at -- we also found terms in terms of suicidal ideation that were picked up, but those terms, since those individuals were not hospitalized for the particular event, it was not forwarded to the SMB. However, that information, if it was a suicidal ideation, it was picked up as an adverse event in the I think it was CBR8, from Dr. Kane's presentation -- would you put it up, please?

(Slide)

This is where those reports of suicidal ideation would have been captured in terms of the patients in the Clozaril group and the number of patients in the Zyprexa group.

DR. LAUGHREN: I guess my question is, is it possible that this other information that somehow didn't get into the electronic database -- for example, nurses notes or a hospitalization at another site -- that somehow might not have found its way into the database that you were using to do the search.

MR. RAWLS: We reviewed all their comments or the comments that would have been captured at the

site. They would have been entered into comments database. We didn't have the actual -- I mean, the clinical history or the information at the particular site in terms of source documents, but that information was part of the case report form. So, I think we had the complete record for the particular patient.

DR. ZANINELLI: I think it's very important to emphasize this was not a purely electronic database comparison. Where the terms were matched in the database, you went to the hard copy. So, it was really a hard copy review which contained all the extraneous notes from staff investigators and anyone involved with the patient.

DR. OREN: Dr. Malone.

DR. MALONE: I think one of the concerns I have is if you have -- if you show that olanzapine is better than Clozaril, it could be that, for instance, olanzapine makes suicide worse, and it's hard to tell what that means about Clozaril. Is there any way to estimate what the, say, rate of hospitalization for schizophrenics is over a two-year period, from large databases, like Medicaid or Medicare databases?

DR. KANE: I think that's certainly a

reasonable question, but there's no evidence that that's the case. I think if you look at the rate of attempted suicides and rate of completed suicides in both the olanzapine-treated group and the Clozaril-treated group in this study, and compare it to data from, for example, the Kahn (phonetic) data that was referred to earlier, that the rates in both categories are extremely low. So, it would appear that there was an improvement that took place in both groups in that sense, although despite that, we're able to demonstrate a significant difference favoring Clozaril. So, there's no evidence when you compare these data to the data from other studies, that the patients in the Zyprexa-treated group were experiencing more events in any one of those categories.

DR. MELTZER: There no data that can really compare with this group. The annual rate of suicide attempts for the whole sample, even though only 80 percent had an event within the three years, was approximately 20 percent per year, and during the course of the study that rate was reduced dramatically in both groups. So there was no evidence that Zyprexa -- if you want to do that pre/post which has a lot of problems associated with it -- but clearly there was

no signal that Zyprexa made for increased suicidal behavior.

DR. OREN: Dr. Winoker.

DR. WINOKER: I'm going to have a few questions. The first two, I just want to have a chance to hear from the sponsor on a couple of issues that in the FDA review that was passed along to us were raised, that I don't think have so far been commented on.

One is the issue of the amendment that allowed subjects to be off-protocol for a period of time and then re-enter again, and in your analysis how that affected the overall.

DR. ZANINELLI: Do we have an analysis of the number of patients who left the study and came back, or an overview? I know there were relatively few.

(Slide)

DR. ISLAM: We have 158. This is our analysis excluding all data after the patient discontinued. So, if the patient discontinued like an RD or came back as an RD or something like that. So, we still have much more significant result.

DR. WINOKER: I'm not talking about the Retrieved Dropouts. I believe it was mentioned that

at a certain point there was an amendment that actually allowed subjects who had been enrolled and then for some reason were out of the protocol, to be resumed under original treatment modality and be included in the primary data analysis, if I'm right in understanding that.

DR. ISLAM: We do not have any separate analysis for this, we just considered that period of time that the patient didn't take drug.

DR. WINOKER: Do we have a sense of how many subjects would have been in that group?

DR. ZANINELLI: Twelve patients overall who left and came back, so I think it's like 8 in one group and 6 in the other -- or 4 in the other. I don't know which way it went, but it was a very small number of patients.

DR. WINOKER: There was another point that was raised -- and, again, just to hear the comment about the change in greater that occurred across two years, and whether that may have had an impact on the CGI-SS assessments.

DR. ZANINELLI: Okay. We did look at that. So the question refers to the fact that over the course of the two-year study, hot many patients in both groups had a change in blinded assessor.

(Slide)

So this analysis looks at the incidence of change in the blinded psychiatrists with regard to the worsening on the CGI-SS-BP. So, in the worsening, we find the score of 6 or 7. No impact was seen -- who did this one? Whose slide is this? I thought we did an analysis -- we'll have to come back to that one. I'm sure the analysis is in there somewhere, as well as the specific question.

DR. WINOKER: I'm coming back to the adjunctive treatment issue. For the antipsychotics, you showed the dose equivalents in terms of Haloperidol. I was curious about the -- well, two things -- the percentage of patients who got adjunctive antipsychotics in terms of typical and atypicals, and if you have any kind of at least qualitative feel for what led to adding an additional antipsychotic. I mean, obviously, on the face, it was for lack of efficacy, I would assume, but if there's any sense of what actually tended to drive adding -- because so many of the patients were on adjunctive antipsychotics.

DR. ZANINELLI: To answer the second question -- while you're looking for the analysis, I believe there was analysis of the first question. But

could we look at the curves for the concomitant medications, please, the mean dose over time.

(Slide)

So, in case of the antipsychotics here, this gives you a little bit of the idea. In both groups, the concomitant medication, which was probably the previous medication, was discontinued. At a relatively early point in the study, however, it bottomed-out for both groups, at a lower level for Clozaril than for Zyprexa. We take this to mean that the patients who were either going on to a new adjunct and staying there, or they are coming off a previous one and staying there, for whatever reason -- you can speculate on the reasons for that. John, do you want to say anything about this?

DR. KANE: I think part of this is a result of the fact that the clinicians treating these patients were given absolutely leeway to do anything that he or she felt was appropriate, and that was a very important aspect of the safety in this study. So, I'm sure there are a number of different clinical reasons that one could imagine. A portion of these patients were also considered to be treatment-resistant, 25 percent. So, you can envision in some cases the dose being increased for that reason, but It

think there were a variety of factors.

And I guess what I would emphasize is that despite this extremely liberal policy in bringing to bear whatever adjunctive treatment anyone wished, that we're still seeing the drug effect of interest.

DR. WINOKER: I think this question will be for Dr. Meltzer, and this is kind of indulging myself. I realize that the driving force in conducting this study was the retrospective analysis that suggested strongly that there was a reduction in suicide behavior in patients looked at, who had previously been treated with Clozaril in the retrospective database.

Apart from the empirical information, which I know is the driving factor here, is there any theoretical reason that intrigues you in terms of why there might be the kind of difference between Clozaril and another sort of cutting edge "atypical" antipsychotic that we should be seeing this kind of difference in efficacy on this measure?

DR. MELTZER: I think there are both qualitative and quantitative signals that could be explored, but it really would be very speculative. On a qualitative difference, there are significant receptor differences -- for example, in terms of 5HT6

and 7 antagonism with olanzapine having no blockade of a 5HT7 receptor and Clozaril blocking it, and they both were effective antagonists of the 5HT6.

My own personal bias is perhaps more toward the qualitative mechanism which looks at their relative abilities to enhance dopaminergic activity in the pre-frontal cortex versus the limbic system, although they both pull it in the same direction, the ability of Clozaril to enhance dopaminergic function in the cortex and the hippocampus is much more significant. And I think they are increasing evidence for a relationship of dopamine to depression, and my own personal -- again, very speculative -- but based on analysis that we did from the Cleveland sample and some preliminary things we're looking here, it's the depressive feelings, feelings of hopelessness, that seem to drive the suicide attempt, which I think, by the way, goes back to the previous question about the difference between the CGI ratings and the event.

What happens clinically, that I've seen, is the urge to deal with extremely distressing feelings can come up fairly rapidly and impulsively, and people act out and make an attempt. And it seems in some way that the Clozaril is preventing that from happening much more frequently than other drugs.

I would also add just one other thing, Andy, which is we still don't understand why Clozaril is so much more effective in treatment-resistant patients in the old sense. That remains an enigma. So much else has been figured out, and perhaps in some ways they're related, but I remain convinced that this is a separate signal.

DR. OREN: I don't want us to stop thinking about psychopharmacology, but for the next 15 minutes perhaps we can switch to considering the psychopharmacology of caffeine instead of clozapine. So, we will take a break now, and return in 15 minutes.

(Whereupon, a short recess was taken.)

DR. OREN: I know there are further questions from our panel, and Novartis also asked for a couple of minutes to address a couple of previous points. So, what we'll do now is I'm going to invite Novartis to take a couple of minutes to respond to some points that were made earlier, and then we will proceed to the presentation from the FDA. There will be plenty of time later for panelists to ask additional questions.

DR. ZANINELLI: There was one question from Dr. Winoker regarding the use of typical and

atypical medications, antipsychotics in the two treatment groups. I pulled this from the listings now.

About half of the patients in each treatment group had atypical or typical antipsychotics during some point during the study. The mean dose in the Clozaril group for atypical -- and these are dose equivalents, Haloperidol equivalents -- for typical was 2.14 mg, for atypical 1.37 mg. For the Zyprexa group, there was the mean dose of typical antipsychotics was 4.26 and of atypical 1.37, so no difference in the use of atypical antipsychotics and typical.

Then there was a question regarding the possible influence of the change in the blinded psychiatrists who rated the CGI-SS -- can I have the slide, please -- and I'll decipher the information on the slide by simplifying.

(Slide)

So all told, there were 13 cases in the Clozaril and 8 cases in the Zyprexa group where there was a change in the BP in a patient who experienced a Type 2 event. So Type 2 event, the main definition was a worsening, on the CGI-SS, a score of 6 or 7. Again, the 13 patients in Clozaril and 18 in Zyprexa

group who had a change in blinded psychiatrist.

The blinded psychiatrist change occurred after the Type 2 event, so after the original blinded psychiatrist had rated the patient, in 7 of the Clozaril cases and 5 of the Zyprexa cases, so more than half of them, or about half of them.

The change at the assessment of a Type 2 event occurred in 6 Clozaril patients and 3 Zyprexa patients after the change in blinded psychiatrist. These numbers are pretty small here, so I don't think they affected the analysis, ultimately.

DR. KRISHNAN: Completely addressing a couple of the questions that we asked, one question was what were the questions asked of patients at each visit -- vital signs, et cetera -- because the question -- there were two questions asked: How are you doing? And, second, did anything happen since the last visit -- which is required by the study design to be asked at each visit, trying to capture as much as you can if anything else had happened during -- and looking through the notes, there was one particular instance where somebody had mainly elicited it during that questioning, that an event had happened. And I can remember at least a couple of those instances from the notes that came through.

The second thing that I just briefly wanted to address again is the medication used. So, keep in mind, during that first phase, that's when most of the concomitant medication use is happening because that's when people are being tapered off and being restarted on this drug. So, that's the period when there is an overlap. So, if you look at the antipsychotic group, that's when you see most of the period, and you can see it rapidly dropping down as those drugs were removed. And I think that's important to keep in mind. It's not a question of using during the course at any high rate, it's mostly in that period of time.

The third one which I think you asked was the diagnostic issue of how the diagnoses were made, et cetera. One of the things you've got to keep in mind is most of these patients, when you read through the documentation -- at least for the ones that I reviewed for the thing -- these are patients being followed by the clinic, these are not advertised patients. These are not patients coming right out of the street. They are being followed by the clinic because these are high-risk patients, so they know these patients very well. And I think one of the reasons that you see a lot of the additional

documentation of co-morbidity, et cetera, comes from that pattern of usage. But there was no formal SCHD kind of interview to make the diagnosis. Thank you.

DR. OREN: Thank you. I'd now like to call on Dr. Khin, from the FDA.

DR. KHIN: As part of Division of Scientific Investigations, we've been involved when the application came in. We've done site inspections for routine data audit as part of the application, according to our Compliance Program.

In addition to this, Dr. Laughren and Dr. Katz, the team has requested that we get involved looking at the specific issues that I believe we've been discussing this morning.

(Slide)

One aspect that we were interested to look at is the Type 1 event. As it's defined, it's the occurrence of a significant suicide attempt, including completed suicide or hospitalization due to imminent suicide risk, including increased level of surveillance. It is as confirmed by the Suicide Monitoring Board.

(Slide)

What is the particular concern that we are going to look at, that was potential bias. As you all

know, the unblinded investigators at each site apparently had the final say whether or not a particular patient event would be referred to the Suicide Monitoring Board.

(Slide)

The purpose of our audit was we were going to look at a subset of clinical records from Clozaril group for whom events were not referred to the Suicide Monitoring Board in order to determine definitively whether or not potential events were ignored for subjects assigned to clozapine. In short, I'm going to refer during the talk as the "non-referrals". So, we are going to discuss mainly non-referrals, we are not going to discuss about referrals.

So, what we did was the Review Division has selected centers with high rates of non-referrals to the Suicide Monitoring Board among the clozapine-treated subjects.

(Slide)

To date, I have looked at two different centers, let's say Center A and Center B. Center A has 14 subjects enrolled for Clozaril group. Out of that 14 subjects, 12 subjects did not have any event referred to the SMB. For Site B, 10 out of 10 Clozaril subjects did not have referral.

On the other site, you might be interested in how about the olanzapine group. For Center A olanzapine group, we have 4 subjects had event out of 14 subjects, and for Center B, and then all the subjects on olanzapine group did not have any events referred.

So, what I did was this morning we were interested in looking at how the information got referred to the Suicide Monitoring Board, so first we are interested to look at the source document itself. So, both non-referral subjects, we went and looked at a source document at the site, which includes progress notes, hospital notes, including ER visits if there are any consultees on site involvement of in-patient hospitalization involvement, we were looking at those notes.

There is a little bit difference between the style among the centers, particularly Center B used like a worksheet style documentation. So, Center B will write for each subject whenever they come in every week or every two weeks, they have already printed out: Do you have any events? Did you go to any outpatient visit for medical reason, psychiatric reason? Are you going to treatment program? Do you have any hospitalization, et cetera.

In addition to looking at the source document, we also interviewed some unblinded and blinded psychiatrists at those sites, but because of the time lapse, some of the blinded psychiatrists and study coordinators have already left the study site.

Basically, out of those 12 subject non-referrals, only 4 subjects completed the study. Eight subjects were discontinued from the study. For the Center B, 5 subjects completed and 5 subjects discontinued during the study.

(Slide)

This is a busy slide, but it's just for a reminder for me. One thing that I want to point out is look at Center B. At week 4, the subject was discontinued, but when you look at the subject source records, the subject was hospitalized for exacerbation of psychotic symptoms. When I went and looked at the study source document, we also look at ER visit, nurses note, including medical student, the whole academic setting, whatever they have, together with the source document.

But in contrast, if you look at Center A, there are some patients that if you look at 1 subject at the bottom, there are some progress notes missing, and you will see 1 subject that there was no-show, and

they tried to contact the subject, and they sent certified mail and the mail was returned. So we see different scenarios of events going in both centers.

(Slide)

In summary, when I look at all the 22 subjects' records, there was no underreporting of Type 1 events. But one thing that I would like to bring to mind is that there is limitation to the inspections.

(Slide)

As we were talking this morning about how information was processed, the subjects were the ones who would report to the unblinded psychiatrist or the blinded psychiatrists during the visits whether they have any suicidal thoughts or events. So, if the subject did not reveal any events during the visits, we wouldn't see any notes.

The other point is the unblinded psychiatrists, even after the patients report any events, they have to use their clinical judgment whether to decide it's a suicide event or not. So, if the unblinded psychiatrist did not report any event, then I won't be able to find it.

And one point I would like to mention is it's limited time and resources. Even after reviewing all these source documents, we didn't follow up any

subjects during the inspection. And, also, the number of records that we looked at is approximately pretty small for Clozaril subjects, there were 368 non-referral patients, and we only looked at approximately 6 percent. And these are all U.S. sites only.

DR. OREN: Do members of the panel have any questions for Dr. Khin?

DR. MEHTA: Do you know if Novartis conducted their own internal audit? You conducted audit of about 6 percent of U.S. patients. They probably might have done it. So the total number of patient records which have been audited independently might be a much higher percent.

DR. KHIN: I think Novartis might be able to answer that question better, but according to my understanding, it is mainly looking at the database. So, what is reported in CRF, and they are looking through the database into the CRF, what is different with my inspection was we look at the source documents, so it's like going to the center and looking at the progress notes and hospitalization notes right at the center.

DR. MEHTA: I think the company audit will probably include the type of document that you're talking about, plus the clinical research associates

monitoring reports and things of that type. Am I wrong here?

DR. COX: Kevin Cox, from Inginex. Yes, our clinical research associates did 100 percent source documentation of everything that was in the CRF at the sites. In addition, they were asked to look at source notes to see if anything was missed, with particular focus on hospitalized patients who may have had increased surveillance.

DR. MEHTA: What percent of patients are audited? I'm talking about in terms of audit, not monitoring.

DR. KANE: I just wanted to put this in a sort of clinical perspective because I think it's important to recognize that this is a rather unique population and a rather unusual study.

The most frequent source of litigation against psychiatrists is suicidal behavior. You know, it's rare where we're engaged in a study where there's a tremendous incentive from the environment, if you will, to get it right. The notion that someone would be biased in terms of reporting or not reporting a suicidal event or suicidal ideation is very different in this kind of context. I just want to emphasize that. It would be hard to do justice to the level of

anxiety of the clinicians who participated in this study because my department was one of them.

You know, many of us are extremely uncomfortable treating a few individuals at this high a risk, and we know that in schizophrenia suicide can be very unpredictable and very lethal. So, I just want to convey a sense of the context because I know that understanding we're biased might enter into this is very important, but there's another element that's at-play in the treatment of these patients, and that's really the anxiety on the part of clinicians to make sure that they get it right, above and beyond anything to do with the research. And if something goes wrong in the context of a research study, it's even worse. So, I just want to kind of give you that perspective.

DR. OREN: Dr. Laughren.

DR. LAUGHREN: Just one brief follow-up comment. Ni, you might mention what your future plans are in terms of completing the sample.

DR. KHIN: For sampling size, we're thinking about we would go up to like approximately 10 percent.

DR. LAUGHREN: When you say you're thinking about that, does that mean that's going to happen?

DR. KHIN: We can't say.

(Laughter.)

MR. RAWLS: I just want to come back to Dr. Mehta's question regarding our audits. James Rawls, once again, from Regulatory Affairs.

We did conduct an audit at the highest enrolling centers after the study had been completed. It was a review to see that all events were reported, and we did not find any additional events, but that was at the highest enrolling centers in the U.S. and in Europe.

DR. OREN: Other questions for Dr. Khin?

(No response.)

At this point, I'd like to turn to the Open Public Hearing part of this agenda, and the first person is James McNulty, President of the National Alliance for the Mentally Ill.

MR. McNULTY: Mr. Chairman, distinguished members of the panel. My name is Jim McNulty and I am the President of the National Alliance for the Mentally Ill. With more than 220,000 members and 1,200 state and local affiliates, NAMI is the nation's largest grassroots organization dedicated to improving the lives of people with severe mental illnesses. I very much appreciate this opportunity to testify

before you today.

schizophrenia is a brain disorder that affects approximately two million Americans. schizophrenia is one of the most devastating and debilitating of all severe mental illnesses. The positive or "psychotic" symptoms of schizophrenia, including delusions and hallucinations, are excruciatingly painful and debilitating for those who experience them. Numerous studies have revealed that the majority of individuals with schizophrenia do not have access to even minimally adequate treatment. The consequences of lack of treatment or inadequate treatment for schizophrenia can be devastating -- homelessness, arrests, incarceration, or suicides.

The 1999 report of the U.S. Surgeon General revealed that mortality rates among persons with schizophrenia are significantly higher than that of the general population. The single largest contributor to this excess death rate is suicide. Studies reveal that 10 to 15 percent of all people with schizophrenia commit suicide. Many others attempt suicide or regularly experience suicidal thoughts. The human toll for individuals who suffer from schizophrenia and their family members is incalculable.

Just an aside, I received an e-mail this morning as a result of a anti-stigma e-mailing that we send out to our members on a regular basis -- this one for Halloween -- and, again, this family member sent me a story of how her nephew had committed suicide three years ago, a young man who was suffering from schizophrenia, and this is something -- she is a mental health professional, and yet nothing that she or her family were able to do was able to prevent this tragedy.

The tragedy of suicide is compounded even further because schizophrenia we know is very treatable today. New anti-psychotic medications, coupled with psychosocial rehabilitation services and supports, make recovery very possible for most people who suffer from this brain disorder. I personally know many people with schizophrenia who have recovered from the depths of despair and today are living independently, productively and with dignity in their communities.

Research has played a key role in facilitating the miracle of recovery for these individuals. Now, research is yielding even more promising information. The International Suicide Prevention Trial is a landmark study that confirms

that Clozaril, an atypical antipsychotic medication first approved in 1990, can significantly reduce the risk of suicidal behavior or suicide attempts among individuals suffering from schizophrenia or schizoaffective disorder.

For NAMI, news about any medication that reduces the risk of suicide or other tragic consequences of schizophrenia or schizoaffective disorder is welcomed. The costs of inadequate treatment of schizophrenia and other brain disorders are immense. The benefits of developing new treatments for these brain disorders are immeasurable. These benefits accrue not only to consumers, but to their families and to society as a whole.

The International Suicide Prevention Trial vividly illustrates the benefits of continuing research on medications after they are approved and on the market. Ongoing research is our best hope for unraveling the mysteries of brain disorders such as schizophrenia and restoring dignity and hope to those individuals who suffer from them. It is equally important to translate the promises of research into practice through rapid approval of medications shown through research to be effective. NAMI is very grateful to the FDA for its efforts over the years to

expedite the entry of new medications for the treatment of severe mental illnesses into the marketplace, after careful study of the safety and effectiveness of these medications.

Finally, I would like to take this opportunity to make one quick editorial comment. Budget deficits in most states and at the federal level threaten the continuing availability and accessibility of the most promising medications for the treatment of schizophrenia and other severe mental illnesses in the marketplace. While we appreciate the importance of balancing budgets, cost containment strategies that threaten access to potentially lifesaving medications for severe mental illnesses do more harm than good in the long run. The hope generated by important studies such as the International Suicide Prevention Trial will only be realized if we successfully forestall these misguided cost containment efforts.

Thank you for affording me this opportunity to testify. I look forward to your questions and comments.

DR. OREN: Any questions for Mr. McNulty from the panel?

(No response.)

Thank you, sir.

Our next registered member of the public is Dr. David Goldman. In contrast to what's listed on the formal agenda, I think he's appearing here in the capacity as a private citizen.

DR. GOLDMAN: That's correct, and thank you very much for taking this public comment. I'm David Goldman. I'm Chief of the Neurogenetics Lab in one of the NIH Institutes, but I'm here representing my family and not in any official capacity. To my knowledge, NIH has no stance on the issue of clozapine licensing or availability.

We welcome the results of the InterSePT trial, which does demonstrate, from what we've seen this morning, efficacy of this drug on suicide attempts. It's representative of the science-based approach which is so critical to the Division of Regulations, and it is also representative of the way that FDA and industry can work cooperatively in scientific partnership.

It's very important to keep in mind that there's a long way to go, however, when we look at the results of this trial and we see that still, after two years of treatment, that there's still 5 suicides out of approximately 500 individuals in the clozapine

treatment group.

The dominating clinical issue in clozapine remains the requirement for hematological monitoring in the administration of this drug and, indeed, that is the greatest barrier to the widespread application of clozapine in schizophrenia even though, as has been pointed out by John Kane and others, clozapine remains the most efficacious antipsychotic medication on the market and available.

That program of hematologic monitoring requiring a complete blood count every two weeks even in patients who have been treated long-term with clozapine is out of step with the science.

Neutropenia occurs early or rarely, and it is very rare in patients treated with clozapine for more than six months. In fact, the indication for hematologic monitoring is different in England where it's once every month, and in certain other countries there's no requirement for hematologic monitoring after six months. So, this ritual of bleeding -- my relative, who has schizophrenia, has actually been treated for about a decade, and has been bled some 350 times, is virtually medieval in its unnecessariness.

It's notable that in the InterSePT study, that despite the impulse to make the clozapine and

olanzapine groups as similar as possible, that the patients treated with olanzapine were, in fact, not bled weekly. And, of course, the effects of this weekly bleeding, I believe, are negative, but I suppose it's also possible that the findings with suicidality could have been colored in some way by the fact that the patients treated with Zyprexa did not receive this weekly venepuncture. I'll leave it to the panel of experts here and in clinical trials on schizophrenia to evaluate the results from the Zyprexa trial.

The only notable difference that I saw was a difference which I again believe just reflects the clinical efficacy of clozapine and emphasizes the underprescribed nature of clozapine, and that is that the olanzapine group was treated with far more ancillary medications than was the clozapine group. So the efficacy of clozapine achieved -- equal in this study to olanzapine, but achieved without the use of the ancillary medications to the same extent.

And so in conclusion, I hope that the FDA working with Novartis will extend their science-based approach to the regulation of clozapine to the most critical issue in the clinical use of clozapine, namely, the hematologic monitoring. Thank you.

DR. OREN: Thank you, Dr. Goldman.

Are there any questions from the Panel to Dr. Goldman?

(No response.)

Thank you.

DR. GOLDMAN: Thank you very much.

DR. OREN: Is there any member of the general public who wishes to make a statement in regard to the matters we're discussing today?

(No response.)

Seeing no further comments, we'll move to the next segment of the agenda, which is for the Panelists to ask questions of the FDA and to begin our discussion. We have a set of six issues that the FDA has requested our discussion and feedback, plus a formal vote. And I'd like to go through those question-by-question, but perhaps before we start that, I know Dr. Ryan may have some leftover questions from this morning.

DR. RYAN: I had a couple, I just didn't raise my hand quite soon enough. The first one I wanted to get clear is on the concomitant meds, Slide CBR-9. That's averaged across all subjects in the study, or all subjects who got a concomitant med in that class?

DR. ZANINELLI: That's averaged across all subjects who received concomitant medication.

DR. RYAN: My second question was just to make sure I understood the analysis correctly. On the WLW analysis, that takes into account the first Type 1 event that a subject experiences and the first Type 2 event that subject experiences, obviously understanding the nesting you were talking about before, but would not -- that analysis doesn't use the subsequent Type 1 or Type 2 events, is that correct?

DR. ZANINELLI: That is correct.

DR. RYAN: On Slide EF-198 that was showing the analysis if you truncated them when they dropped out of the study, is that easy to pull up? It was something around 198. Is that easy to pull up?

DR. ZANINELLI: 198?

DR. RYAN: I believe I have the number correct. It was the question on the people who left the study.

DR. ZANINELLI: Maybe it was 158.

DR. RYAN: 158 -- my apologies.

(Slide)

That was it, yes. On the Type 2 one down at the bottom, you have a p-value of .005, but the confidence interval goes to .99, is there a typo on

that?

DR. ZANINELLI: Um-hmm.

DR. RYAN: The confidence interval has a ratio that almost goes to 1, but you've got a p-value of .005, so that looks incorrect.

DR. ZANINELLI: We will check that.

DR. RYAN: The final one, and probably the only substantive one since I'd guessed right on the other things but wasn't sure, can you comment some more on the depression as a side-effect which also differed between the two treatment groups, as did the suicidality as a side-effect, and how that correlated with the actual suicide attempts because, obviously, as you talked about, your depression measures and your suicidal measures which didn't correlate with anything, but did depression as a side-effect -- the question was the side-effect was more frequent in the group that had also more suicide attempts. Did the two correlate?

DR. ZANINELLI: Dr. Krishnan?

DR. KRISHNAN: Just very briefly, if you model it for the purposes of effort-based analysis, which -- this is a very rich dataset, by the way, it allows you a lot of things you could do -- yes, there are a few mediating variables prior to the suicide

attempt, and the mediating variables appear to be drug abuse, alcohol abuse, as well as depression. Worsening of those things predicts events, both hospitalization as well as -- but it's epoch-based, it's just before. If you look at an epoch, it seems to predict it. Remember, that these are not done cross-sectionally, so you don't have event-to-event, you're really looking at epoch of the event.

The other interesting thing is negative symptoms also have an interesting interaction, but there are a lot of things that have to be explored with it, rather than making any definitive statements at this point.

DR. RYAN: Thanks.

DR. OREN: Dr. Rudorfer.

DR. RUDORFER: Just a follow-up question to that. Are there any data on the extent that patients in either group developed full major depressive episodes as opposed to just a score on the depressive symptom?

DR. ZANINELLI: No, that information wasn't collected, so reason for dropout did not include these as specific diagnosis if it was a psychiatric condition or not. So, we don't have that information.

DR. OREN: Dr. Cook.

DR. COOK: I'd like to -- in thinking about the Type 2 events, I wonder if you analyzed -- the analysis of adding the Type 2 defined events, or what's added when you go to Type 2, is so confounded by the Type 1 baseline. What I'd like to know is the analysis of worsening of suicidality is measured by CGI-SS-BP score of 6 or 7 in the two groups, and not having the Type 1s confounding that analysis.

DR. ZANINELLI: Comparing the 18 and 20.

DR. COOK: No, because -- what I want is the ones that would have been defined as Type 2 had they not -- irrespective of whether they were Type 1 or not. Does that make sense yet?

DR. ZANINELLI: But that would be those 18 and 20 --

DR. COOK: No, there are more than that. One would presume that of the ones hospitalized, many of them still had a worsening on the CGI-SS-BP. Does that make sense?

DR. ZANINELLI: So you're saying irrespective of whether it was a Type 1 and Type 2 event or not, whether -- if they had a worsening, so the analysis of that --

DR. COOK: Basically, in your Type 1s,

presumably there are many subjects that had they not met the criteria for Type 1, would have met the criteria for Type 2.

DR. ZANINELLI: Were the analysis based on first event, so it's a Type 1 or Type 2 event, do I understand?

DR. COOK: No. In a sense, you are only analyzing those that did not have a Type 1 and saying that they had a Type 2, I assume, because you don't have overlapping distributions there. So, what I'm getting at here is when you analyze the CGI-SS-BP score, basically you showed us a difference from baseline to 104 weeks. That's much different analysis than the survival analysis you did with Type 1 and Type 2, as you defined them.

So, I'm very interested in the discrepancy there, that troubles me. What I would like to know is what happened with the CGI-SS-BP score if you submitted just that to the same kind of survival analysis.

DR. ZANINELLI: I see. The analysis of the secondary variable.

DR. COOK: Well, that's not how it was defined in the material I got from the FDA. So you're saying that was secondary, what I got from the FDA is

that you had two primary endpoints, so this becomes very important. It's particularly important because it is the blinded rating, and that's important to me.

DR. ISLAM: Unfortunately, we do not have that prepared now, just for that CGI-SS -- time to worsening of CGI-SS 6 or 7. That's what I think you want.

DR. COOK: I mean, you have that for the ones that weren't Type 1.

DR. ISLAM: Right.

DR. COOK: So I don't understand why you don't have that for the ones that are Type 1.

DR. ISLAM: Because we define Type 2 as the correlation of CGI-SS in Type 1. That's why we present a Type 2 as combined.

DR. COOK: I can't imagine that that would be that hard to retrieve.

DR. ISLAM: It's not hard, we just do not have any slide prepared for that, that's what I'm saying. It's not hard at all.

DR. OREN: Dr. Katz.

DR. KATZ: I have one more question about the retrieved dropouts. You showed some information about those patients. Maybe you've already said this. When you retrieved them, did you only retrieve them at

Week 104, or did you evaluate them at what would have been their perspective study evaluation time point?

DR. ZANINELLI: So it was date of retrieval then ongoing and not just at the endpoint.

DR. KATZ: Right, it was adjusted at the end when they would have completed 104 weeks.

DR. ZANINELLI: The question is whether the retrieved dropouts, the date of retrieval was only at the end of their respective endpoint or during the study. So my understanding is also that at the -- periodically, data was retrieved from those patients that discontinued.

DR. KATZ: It was retrieved.

DR. ZANINELLI: It was retrieved.

DR. KATZ: At what would have been their study visits, had they continued.

DR. ZANINELLI: Yes.

DR. KATZ: And I notice that there were 12 clozapine patients who had a Type 1 event and 3 Zyprexa patients, if I remember the little footnote, out of, I think, 60 retrieved dropouts in each group, if that number was correct.

DR. ZANINELLI: Yes.

DR. KATZ: Do you know anything about the timing of those events in relation to when the drug

was discontinued, in each of those cases?

DR. ZANINELLI: The timing of the Type 1 events in the retrieved dropouts, do we have a distribution of that? No, not right now.

DR. KATZ: Is that something you could recreate, not necessarily by the end of the day, but --

DR. ZANINELLI: Yes.

DR. KATZ: Thanks.

DR. OREN: Any other questions from the Panel towards the sponsor or towards the FDA? Dr. Rudorfer.

DR. RUDORFER: I just want to clarify one point. As I understand it, other than the recommended doses, the PIs were not given any specific treatment manual or practice guidelines. During the course of the medical monitoring, was there any judgment made or correction made in terms of the clinical interventions being used -- for instance, whether concomitant medications seemed appropriate, or how they were used, or dosage?

DR. KRISHNAN: There were no strengths on those interventions deemed necessary by the Principal Investigator to maintain patient safety. So, hospitalization concomitant medication was done if the

Principal Investigator said it was necessary, and there was no interference from sponsor or from medical monitor with respect to these interventions.

DR. RUDORFER: If I could just make an observation because I don't think we should let the morning end without it. Concomitant medications, in my view, are potentially a two-way street here, and they don't always work out as planned. Antidepressants, which were used quite liberally, certainly can worsen psychosis.

We saw in some of the case material we received -- for instance, at least one case where a patient received Buproprion (phonetic). Now, we're not in a position to judge whether or not that was appropriate, but many people would consider that a high-risk intervention in a psychotic population.

Similarly, going back to some of my earlier concerns about the schizoaffective population, we don't know, for instance, if an antidepressant could have accelerated cycling or induced mania or mixed state in any of the patients, so the fact that some patients received more concomitant medications than others, on its face, I don't know that that's necessarily to those patients' advantage.

DR. KANE: You certainly raise an

important consideration. I think, really, the driving force in the design of this was to give the clinicians as much freedom to do anything that they felt appropriate. Now, of course, you could argue for practice guidelines and so forth, but I think we would have considerable debate as to what those guidelines should say in this context, and whether antidepressants are appropriate or inappropriate.

So, I think what we've seen here is a real-world attempt to allow the clinicians to treat these patients the way they saw fit. If we had not permitted that, I think it would have been extremely difficult to do this study, given the level of anxiety that the clinicians had. If we restricted their choices in any way, they would have felt extremely uncomfortable managing these patients.

I think it's difficult to -- you know, we could debate about the impact of antidepressants or not giving antidepressants or antipsychotics, but what we've seen here is within this kind of real-world framework, the differences are still apparent between the two drugs. The clinicians were doing their best to maximize the treatments that they had available, and despite that we're seeing a difference between Clozaril and Zyprexa, and I think that's very

powerful.

DR. KRISHNAN: Just to briefly address the same issue, it's not just antidepressants, but also the anticonvulsants and Lithium usage was more -- again, it goes to the issue that if you're looking at concomitant drugs and cycling, the pattern was not observed one group to the other. Just look at what all concomitant medications that were used. This is a real-world population that you're using whatever you can to keep them alive, essentially.

DR. OREN: Dr. Hamer.

DR. HAMER: Forgive me if this question has already been answered, but I don't think it has. I'm still curious about the use of olanzapine in the subjects randomized to clozapine, and the reverse. I think that you indicated earlier that most of that took place during the down-titration of whatever a previous medication was, and up-titration of whatever the randomized study medication was. Do you have any figures on how many patients during the course of the study, after down- and up-titration, were actually given the opposite drug as a concomitant medication?

DR. ZANINELLI: No, we don't at this time, but that would also include patients who -- the retrieved dropouts, for instance, who really

discontinued before participation were being followed up for endpoints -- may have been on both study medications as well. I know there were a couple of cases of that. We don't have a listing of the breakout of that.

DR. OREN: Dr. Hamer.

DR. HAMER: Let me ask a follow-up question. From your familiarity with the actual subjects and case reports, were there, in fact, subjects who were randomized to one of the two study medications during the study, and then the treating psychiatrist decided to prescribe exactly the other medication for clinical purposes?

DR. ZANINELLI: The database shows that two patients were randomized to Clozaril, but actually received Zyprexa.

DR. HAMER: As a concomitant medication or as a protocol violation?

DR. ZANINELLI: It's a protocol violation, so instead of the assigned drug.

DR. HAMER: Thank you.

DR. OREN: Okay. Members of the Panel are still welcome to ask questions of whoever will know the answer, as we go through our discussion, and I want to invite every member of the Panel to feel very

free and welcome to speak up and commenting on any of the questions that we go through.

So the first identified issue that the FDA wanted us specifically to provide some discussion and feedback on regards potential bias in referral of events to the Safety Monitoring Board. Dr. Katz.

DR. KATZ: I wonder if I could sort of broaden that question a little bit because I notice that one question that we have not explicitly put on the list has to do with the general issue of the unblinded nature of the accumulation of the primary data. Obviously, the primary outcomes were assessed on the basis of a blinded review of data that was recorded in an unblinded way, and Dr. Khin mentioned briefly and Dr. Khin addressed briefly, the question of the possibility that for whatever reason the data were recorded in such a way to minimize the number of events attributed to clozapine.

So, I would be interested in a broader discussion of the lack of blinding in the recording of the primary data which, again, could have had an effect in what was recorded in the first place, and the vigor, if you will, of how the unblinded Principal Investigators tried to gather data about, let's say, hospitalizations between visits, that sort of thing --

how aggressively they queried retrieved dropouts, that sort of thing, given the unblinded nature of the treatment assignment.

So, we're very interested in the specific answer to the question about potential bias in referrals, but also the larger question of the unblinded nature of the study.

DR. OREN: Dr. Wang.

DR. WANG: There's a third level that the bias could occur not only in the recording of the primary data and the referral to the SMB, but also there's the issue of the SMB itself, and there is one analysis that I had a question about.

It was in response to the FDA, a table was sent showing the proportion of cases that the SMB considered to be a Type 1 event, and then it showed a cross-tabulation that also showed what the blinded psychiatrist thought. And there was a significant across the diagonals -- in other words, there was about 4 percent where the SMB thought it was an event, the blinded psychiatrist did not, in the clozapine patients. But then it was about 12 percent in the Zyprexa patients. Again, 12 percent of the Zyprexa patients were felt to be Type 1 events based on the SMB but not by the blinded psychiatrist.

Could you explain to me -- maybe it's Dr. Krishnan -- why there's this statistically difference in the proportions.

DR. KRISHNAN: Let me just very briefly address what the reasons for the discrepancy could be. There are two possible explanations for this. First is the blinded psychiatrist evaluation of Type 1 event was just his own evaluation, not subject to any challenge. As I said earlier, one of the issues of classifying an event here required pulling together as much information as you can, and doing our own discussions of this, and it took a while to get us to work together to make that classification clear.

Second, there were only three of us making it for every event whereas the blinded psychiatrist just did it for a few events, and there were lots of blinded psychiatrists. So the potential for one blinded psychiatrist to do it differently from another one at another site was quite great.

On the other hand, you should turn it around and look at what is the concurrence that we have, and the concurrence, even if you look at it as 4 percent and 12 percent, the overwhelming majority is high concurrence between the blinded psychiatrists and the SMB Board as a whole.

DR. WANG: High concurrence is -- it's the differential that I'm wondering about.

DR. KRISHNAN: Yes, the differential is there, but you've got to also remember they are blind and we are blind. Whether they could have had a little more unblinding than us, the possibility is yes, because the blinded psychiatrist actually is seeing the patient when he does the ISST evaluations, et cetera. And potentially there is the possibility of unblinding by evaluating the patient, that actually occurred in a few instances where, if you notice, it says some of those patients, blinded psychiatrist data was not used because he became unblinded in the context of seeing the patient.

So, those are the two main key points why -- you've got to remember, the SMB was kept blind, and all that we reviewed were the records that were sent to us. But it's a good question, and why it differentiated between the two? Other than saying it was probably chance, I can't tell you another explanation for it.

DR. WANG: It was highly significant, it wasn't chance. Could I, as long as we're on this issue of bias, address the first issue of whether the referral to the SMB was potentially biased, and I

agree, the analysis that you presented is, on face value, reassuring. It says that if -- I think it was Slide 53. On the surface, it looks like -- if this bias is existing, it looks like it's small in magnitude.

But to feel reassured, I have two other questions regarding that, and that is -- if you show the slide, I can --

(Slide)

DR. KRISHNAN: It's just 1 point here, the concurrence, if you want to look at it, is 90.5 for the first events, the SMB and the blinded psychiatrists, and equal percent if you look at it as all events.

DR. WANG: That's not -- I'm looking for CES-53, if you have that.

(Slide)

The question is, in the 40 percent that -- in the second row, the number of cases with at least 1 search term matched, it looks like about 40 percent across both arms. Could you break that down by arm?

DR. ZANINELLI: For the Clozaril, of this number, it's 115 cases, and for Zyprexa, 164.

DR. WANG: And percents?

DR. ZANINELLI: Percent of the 490 or

percent of the --

DR. WANG: What percent of cases that weren't referred, these non-PEPs, what percent did your search match a term?

DR. ZANINELLI: Oh, 115 of the 701.

DR. WANG: If you take the 279 out of the 701, could you break that down by study arm? I'll tell you why I'm curious. Earlier you said that the review by the sponsor was potentially not blinded. So, in terms of this, this particular percent, it shouldn't be affected by any judgment of a nonblinded reviewer, so that's why I'm just curious if the percents were similar.

DR. ZANINELLI: Well, 279 breaks down to 115, and then -- for Clozaril, for Zyprexa to 164.

(Simultaneous discussion.)

DR. WANG: What percent of Zyprexa patients not referred.

DR. ZANINELLI: Do we know the breakdown of that? We can get that in the course of the session.

DR. WANG: Thank you.

DR. OREN: Dr. Ryan.

DR. RYAN: A quick followup. If you did the analysis based on the blinded psychiatrist

declaring Type 1 events rather than the blinded Board, it also comes out significant and slightly more significant, or did you do that analysis? Because the blinded psychiatrists declared more events in the Zyprexa -- that's for the greatest events that they declared, right?

DR. ZANINELLI: Do we have that? This is the cost analysis for the Type 1 event for the SMB, as seen during my presentation, for the BP alone, and then the cases where there was concordance between the SMB and BP. So the hazard ratio of .86 when the BP does their assessment, the p-value then drops to .236. Does that answer your question?

DR. WANG: Yes.

DR. OREN: I think the update is posing to us a broader question even beyond this specific study, just as far as the general study design, as far as the unblinded nature of the primary data analysis and referral to the Safety Monitoring Board. Do the Panelists have any comments on that?

(No response.)

Is this the kind of thing we'd like to see more of, see less of, improved?

DR. ORTIZ: I guess my initial reaction is that this particular group is such a complicated

clinically-challenging population. We're talking about people with schizophrenia who also have anxiety disorders, who have substance abuse disorders, who have mood disorders, and I think I agree with the sponsor that it would be detrimental to evaluate something like suicidality in this group, without allowing clinicians to use optical psychiatric medications for what they are seeing as needed.

DR. OREN: Dr. Katz.

DR. KATZ: I think that's a slightly different issue from the question of blinding because one could do that in a blinded study as well, I believe. Again, I believe the reason for the lack of blinding was that it was felt that you couldn't, as has been mentioned in several places, draw blood every week from someone who wasn't getting clozapine. So, that automatically would unblind it. So, I think that's what the unblinded design was related to, not the fact that physicians needed to maximally treat. I think you can maximally treat patients in the face of a blinded study.

DR. OREN: Dr. Malone.

DR. MALONE: The case reports were written by the unblinded psychiatrists, that's correct, isn't it? Couldn't you do a design where you had a parallel

thing done by the blinded psychiatrist, that he would write case reports and refer them to the Suicide Monitoring Board? At least you would have a measure of what the blinded psychiatrist thought should be referred versus what the unblinded did. It would be one way to have a blinded referral.

DR. OREN: Anyone else specifically on the blind?

(No response.)

I think there's no loss of sense that blinded studies are the strongest and the best, and balancing that with the real world. Dr. Cook.

DR. COOK: Well, I think there is a standard, and I can imagine this coming up before another committee to review a proposal at NIH, and it comes up in psychotherapy research all the time, for example, and the standard is blinded raters. And I don't know why we would change that. I can imagine many people thinking about various indications that would now become approvable on the basis of studies that are equally hard to do.

So, I have quite a bit of concern, given that there were blinded raters and given that there wasn't an effect seen, but that was a different analysis. I have a lot of concern that analysis of --

a survival analysis with only blinded rater data is not available to us.

DR. OREN: Again, continuing the broader view both with this study and with regard to other studies the FDA may be considering one of the issues is adequacy of the single randomized control trial to support suicidality claim. And maybe for the moment we can focus on the single randomized control trial part of that statement both with regard to this study and the broader question, given that the FDA standard is normally for two randomized control trials. We can focus on the suicidality perhaps a bit down the road in this discussion, but any comments on this? Dr. Ryan.

DR. RYAN: Yes. I've been reflecting -- in child psychopharm studies, you've got a similar issue of, you know, the hazard to people and what you inform them on, and I was wondering, as a family member of a potential participant in this study, if you had -- one trial that came out positive -- if you would seem to have an ethical obligation to tell people going into the second trial, that the first trial had come out positive. That's only one trial, it may or may not constitute evidence. But it's somewhat unclear to me, given the potential disastrous

outcome with suicide, that one could effectively recruit for a second study if ethically investigators are ones who insisted you inform them of a prior study that was deemed to be positive. So, I wonder if we don't have to take an approach like that simply to study these really overarching questions that are hard to recruit for and large, and yet it's hard to know how you'd do a second study, or how you would effectively recruit for a second study, or how you'd representatively recruit for it.

DR. OREN: Ms. Bronstein, you're our Consumer member of our Panel, any thoughts?

MS. BRONSTEIN: I really think it would be very difficult to suppress the information after you have some significant result, and I'm thinking in terms of your patient family members primarily, that really live on a day-to-day basis with this fear, and it would be very difficult not to address that.

DR. OREN: Dr. Winoker.

DR. WINOKER: I think we've also been told the single trial is more something that will be considered when there are additional evidence that would support the claim, and I think -- you know, we've had presentation of additional evidence, albeit retrospective, that certainly speaks to that.

I think this is focusing on an issue of significant public health importance for which the increasing scrutiny of human subjects research makes it extremely challenging to envision and conducting studies like this, with the standards being set ever-increasingly higher for protection of human subjects.

So, I think based on assessment of how these results are viewed, I would view that it would be difficult to still feel that a separate study in this population would be feasible.

DR. OREN: Dr. Hamer.

DR. HAMER: It would be simple to do two studies, just do them both at the same time. That way, you don't have the answer. Sponsors do that all the time.

DR. OREN: Dr. Katz.

DR. KATZ: The other issue, I think, when we're talking about whether or not that in this case a single study plus something called confirmatory evidence is sufficient, I think you have to take into consideration the meaning of the clinical outcome that was assessed here because, in fact, it didn't -- well, we don't know -- but there were very few events of actual completed suicide, so there was no effect on mortality, in that sense, or no differential effect

between the treatments. The effect was on something called "suicidality" as, obviously, defined as you've heard.

So the question is whether or not that endpoint -- which, of course, was a composite endpoint -- whether or not that endpoint is sufficiently known, for example, to be predictive of actual completed suicides to say, well, yes, this one study is sufficient because it's unethical, for example, to do another one because this outcome clearly, for example, is related to actual completed suicides. In this study, it wasn't.

So, I think when we think about is one study enough, I think we have to think about whether or not the outcome that was assessed and on which the effect was shown is an appropriate outcome for that sort of standard to be applied.

DR. OREN: Dr. Meltzer.

DR. MELTZER: In this study, the ratio of serious attempts to completed suicide was about 1 to 10. That is a lower ratio than the literature usually reports. It's usually closer to 1 to 5 in this population. For every 5 serious suicide attempts, one can expect usually in the next year or two at least one completed death in that population.

We did a para-analysis using what we saw in the study. If we had tried to do a study with the same kind of estimates of differences, we would have needed 20,000 patients in order to find a significant difference, with the same small number of deaths as the outcome.

So, I think there are applications for the ultimate mortality by reducing the number of serious suicide attempts.

DR. OREN: Dr. Kane.

DR. KANE: If I could just add to that, I think, in talking about suicide, obviously, that's the most dire outcome, but the effect of suicidal attempts and suicidal behavior is enormous. If you see these patients, if you talk to their families and you see what has happened to them as a result of failed suicide attempts, this is also a source of enormous morbidity, family burden, et cetera, et cetera. So, I feel very comfortable arguing that the prevention of suicidal behavior, the prevention of suicide attempts as a goal, in and of itself is absolutely critical. And it's clear, obviously, that people at highest risk for suicide are the people who have attempted suicide in the past, but I think we can certainly focus on the results in this trial based on suicidal behavior, not

on completed suicides.

DR. OREN: To go off-topic for a moment, I need to take the pulse of the committee with regard to how we proceed from here. We have officially on the schedule a possibility for a lunch break for an hour at this time, and I need to have a sense from the committee if that's something that we should take right now, as scheduled, or if people need some personal time, or if we should keep going and end the meeting at an earlier hour. Any thoughts? Another option would be to take a ten-minute break now and then to discuss further. Dr. Cook.

DR. COOK: I just vote for lunch.

(Laughter.)

DR. OREN: Lunch it is. We'll meet back here then in one hour.

(Whereupon, at 12:10 p.m., the luncheon recess was taken.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:10 p.m.)

DR. OREN: Okay. We have covered clozapine, caffeine, and the last hour proteins and carbohydrates, and now we're back to clozapine, and there are a couple of speakers from Novartis who have just asked for an additional moment to respond to some of the questions asked by the Panel earlier. We'll resume with them, and then we'll resume with our general discussion.

DR. KRISHNAN: The first issue is the blinded psychiatrist and the SMB, and just to give you an idea what the process differences were and who we were, the SMB, as I said, three of us rated everybody, looked at every event. The blinded psychiatrists, there were 68 of them, each site, very few events rated by any one of them.

We spent the first several months making decision points of how we were going to evaluate this, they didn't. There was no training set up for them to learn how they were going to make a decision. That was two critical differences between us and them.

The other thing to keep in mind is a blinded psychiatrist often did not get to rate the event in the same time frame. Sometimes there might

have been a delay before the time they rated it.

And the other piece that there was a greater propensity or potential for them to get unblinded because they were working in the same location, some of them did get unblinded, and they were also seeing the patients. Any of you who have worked with either clozapine or olanzapine patients, it's very difficult to keep the blind, especially in those who are psychotic in nature. Patients who are psychotic are going to say something, and that could always create an issue when the blinding -- whether they consciously or unconsciously do it, that's a factor. That is the reason why, up front, the decision was made that the SMB would be the one on which the final decisions were going to be made on whether it was a Type 1 event or not. So, that's the first piece.

And we also wanted to make sure the SMB was blinded to the experimental treatment, and also the location of the patient, and the packages that we received were anonymized and, therefore, there was no way of us knowing which patients were on clozapine and which were on olanzapine.

The allocation of actual treatments was random, as you know, and therefore any bias to

determine categorization by the SMB would have been random and could not have discriminated between the trial drugs.

The second piece that I wanted to very briefly state again is the rating scales, which I think has come up a couple of times. Two things to remember -- the rating scales were done -- the ISST, CGI-SS -- had designated time frames initially at four weeks and then started to spread out. Therefore, it did not have the same frequency at which events were happening or captured, and one of the things that if you actually look at the scale scores is the time for worsening on a CGI-SS is referring to the week before, and that may not have been a week when anything happened. The patient may actually have been doing better. And, therefore, that instrument does not work as well as the events that they are trying to capture. So, scale not measuring the same thing as an event, and the scale measures more on timed basis which were much less frequent than the events.

DR. OREN: Dr. Kane.

DR. KANE: John Kane, the Zucker Hillside Hospital. I wanted to get back to a question that had come up earlier also, which was the number of patients with a score of 6 or 7 on the CGI-SS-BP, so this is

the Type 2 event, if we could have that.

(Slide)

So we see that among the Clozaril-treated patients, there were 38; among the Zyprexa-treated patients, there were 42. And keep in mind that there were roughly 240 Type 1 events. So the Type 1 event proved to be a much more sensitive indicator of what was going on here, and for the reasons that Ranga just articulated, these assessments were done at fixed intervals, in many cases many, many weeks apart, so the real outcome of interest here, obviously, is the suicidal behavior that occurs at very unpredictable times during the course of followup.

I also just want to emphasize that the outcome measures, the amendments that took place to the protocol, were all done prior to any analyses and were agreed upon with the Agency. So this was a best attempt, I think, to bring a meaningful outcome measure to a very, very difficult population.

DR. ZANINELLI: I just have two brief responses to questions. One was Dr. Wang's question regarding the total number of non-referred cases, what the breakdown here was, 701. So, it was 368 patients in the Clozaril group, and 333 in the Zyprexa group.

And the next one was a slide here that Dr.

Ryan pointed out.

(Slide)

The confidence level was .99, that was incorrect, it is .90. Thank you.

DR. OREN: Okay. I want to turn now to the second issue that the FDA particularly raised about claim focusing on suicidality in schizophrenia or schizoaffective disorder. So, the first part -- Dr. Winoker, do you have a question with regard to that issue?

DR. WINOKER: Kind of as a continuation of the discussion that Dr. Katz had started before the lunch break, I was remembering back to an excellent presentation that Dr. Laughren had given at one of this committee's meetings about a year ago, I think, for the Alzheimer's discussion, and in that meeting Dr. Laughren presented a very nice overview of the fact that the Division now really was wanting to focus on specific and very recognized validated diagnostic entities for indications, and the trend was really to move away from more kind of symptom-based or not specific recognized disorder oriented indications, so I think you briefly touched on that point earlier this morning, as far as being open to this kind of indication. But it seems to me this is kind of the

mirror image of the question about how we feel about these behaviors as sort of surrogates for actual suicide, if you have any perspective on kind of the Division view on this type of indication.

DR. LAUGHREN: Well, I think they're sort of two separate issues. I mean, the one issue was whether or not you can focus on one particular aspect of a well-defined syndrome. And I use as an example ordinarily you wouldn't focus on one of many positive symptoms as the target for a claim. That we would consider, in a sense, a pseudospecific claim. But if you can show that a particular aspect of a disorder responds differently or doesn't respond to usual treatment and does respond to a particular treatment, that might be a legitimate target for a claim. So, it's not that we wouldn't accept focusing on a symptom, it's just that there has to be some justification for it. And if there's a differential effect of drugs on that symptom and it's an important symptom, then it would be a legitimate claim.

But the other question that you raised is whether or not the outcome, the suicidality outcome, in this trial is an acceptable surrogate for the outcome that everyone worries about, which is a completed suicide. That is, I think, a separate issue

that requires some discussion.

DR. OREN: Dr. Hamer.

DR. HAMER: I'm not sure, but I thought I heard someone say -- and it sounded reasonable to me -- that I don't think you need to think of attempted suicides, necessarily, as a surrogate for completed suicides, that there are enough serious consequences to attempted suicides of various sorts that it would be worthwhile addressing attempted suicides, whether or not you actually see a reduction in completed suicides.

DR. LAUGHREN: Yeah, I think that's a fair point and, again, it's something that ought to be part of the general discussion.

DR. OREN: Dr. Rudorfer.

DR. RUDORFER: I want to go back half a step in this discussion. Both of these compounds that we're talking about today are labeled for the treatment of schizophrenia, neither is labeled for the treatment of schizoaffective disorder, so that when we consider suicidality, we're considering that as maybe a secondary or another, an additional potential indication for Clozaril. On the other hand, there is no primary indication in terms of treatment of schizoaffective disorder.

So, I'm quite concerned about that because basic issues of efficacy and safety and dosing, as we've been alluding to, we have no data on in terms of the treatment of schizoaffective disorder. And I don't want to be redundant, but the field remains rather perplexed about what schizoaffective disorder is.

I'm reminded that when Clozaril was first approved under DSM3, there were no diagnostic criteria for schizoaffective disorder because the committee appointed by DSM3 could not agree on what the criteria should be. Every edition of DSM since has a different set of criteria, so they do exist for DSM4, but I don't believe they were properly followed in this study because the DSM4 states that a type should be -- not may be, but should be -- specified because the two types that are commonly recognized by the field may not both correspond as a subtype, if you will, or a relation of schizophrenia.

So, I have a problem with looking at a secondary indication in terms of a disorder, that is not a primary indication.

DR. OREN: Dr. Katz.

DR. KATZ: That's fair enough. I just want to sort of tease out the two -- at least two --

potential issues in what you said. One is whether or not schizoaffective disorder is well enough described and accepted as a diagnostic entity to even grant any sort of a claim for. And the related question is whether or not, if it is, the patients in this study who are called schizoaffective actually meet those criteria. So, that's one issue, the reliability of the diagnostic category.

The other issue is what the claim -- does this study support any sort of a claim in that population? It's quite possible that you could have a claim for suicidality or the reduction of suicidality in a particular diagnostic claim, without a claim that it treats the general symptoms of that claim. And that's what the sponsor has proposed -- it says "for the treatment of suicidality and schizoaffective disorder" -- it's not for the treatment of schizoaffective disorder. You could have such a claim, but it's unusual.

DR. RUDORFER: Right. And, again, for that we've seen no dose response data on that, or toxicity data related to this population specifically.

DR. LAUGHREN: Only what you have in this trial. Of course, it was not a fixed-dose study, so you don't have information on dose response.

But could I get back to your sort of elaborating on Rusty's points. Are you doubting the legitimacy of the diagnosis of schizoaffective disorder, as it is currently defined in DSM4?

DR. RUDORFER: No, but I'm questioning whether that was followed in this study that we're viewing. Again, there were no structured interviews done and, as Dr. Krishnan pointed out, the diagnosis is used somewhat loosely even in this country, let alone around the world, and I'm not sure -- and I made reference to the case that was called "schizomania" -- again, a term which we have not seen in the other materials from the sponsor. I'm just concerned that a large group -- maybe 40 percent of the patients we're talking about -- I'm not sure I really know what's wrong with them.

DR. OREN: Perhaps to help us focus in our discussion, let me ask the committee, and you can shoot me down if this isn't a good way to do it. In some ways, there are two questions that we're talking about here, one is suicidality as an outcome measure and how that should be defined and whether that's acceptable, and the second is the particular subject groups -- schizophrenia, schizoaffective disorder. Would it be worth talking about each separately?

So perhaps then let's stand on the suicidality, and we'll come back to the very important question of the population group. How does suicidality sound as a target measure, and obviously that will tie into labeling issues as well. Dr. Ortiz.

DR. ORTIZ: My concern with suicidality is that it's generally considered a symptom within a mood disorder and generally depression, and that using it in a new and different way is going to have implications for clinicians. And I think my biggest concern is not psychiatrists but, as we've seen with antidepressants, the majority of people using antidepressants are no longer psychiatrists, they are primary care and mid-level providers. And my concern would be how do they -- how would they understand a symptom of depression that's now used in a different context?

DR. OREN: Ms. Bronstein.

DR. RYAN: I might come down perhaps in a different position than what I sense Dr. Ortiz was trying to say, that it's certainly -- of the different aspects of the presentation, that was the one that certainly seemed to make a great deal of sense to me, the argument that this is a -- that suicidality is

separately something one wants to treat, whether or not -- presumably, it's a proxy for a completed suicide, but the argument on power calculations for a study to show a significant decrease in completed suicides, and the costs of such a study might well be prohibitive. And so it seemed like you have both that argument, but also the argument that there's a substantial societal gain to preventing suicide attempts, and that there's at least a rational basis in some prior data to suggest that this -- that some compounds may differentially treat that. So, I pretty much bought that part.

MS. BRONSTEIN: Treating suicidality in psychotic populations is really different than in other populations, and I know we're not on labeling yet, but I think as we're thinking about suicidality as a target to treat, I think it has to be really clear that this be for a psychotic population and not for a general population. And we don't have as many tools to treat psychotic patients as we do for non-psychotic patients. And I think the study is interesting in looking at its effectiveness for this population.

DR. OREN: Dr. Malone, did you have something to comment?

DR. MALONE: I was going to say something similar, that you would want to look at suicide perhaps within different disorders, or that there are different kinds of causes of suicide, so that, for instance, in adolescence, probably mostly those children are -- I mean, those adolescents are maybe taking substances and having impulsive acts, which would be different in someone who is psychotic having a suicide attempt, or at least the treatments would be different. So, if you had impulsive acts because you were on substances, you would stop the substances. But if you had impulsive acts related to psychosis, you might end up using an antipsychotic.

DR. OREN: Dr. Hamer.

DR. HAMER: Generally, this Division has historically been reluctant to approve medications for the treatment of particular symptoms, but you have at least started the slippery slope in terms of things like approval of medications for agitation in dementia. And, also, other Divisions -- I mean, there are clear precedence for approving things like medication for pain, or medication for fever, and the general -- my understanding of the general philosophy is that to do that it generally needs to be demonstrated that the medication is effective for pain

or for fever in the context of several different illnesses, and we don't have that situation here. This reads like treatment for "a" symptom in the context of "an illness".

DR. LAUGHREN: Just to clarify, that is exactly right. We in no sense view this as a nonspecific claim for suicidality. It's clearly in the context of these two specific illnesses.

DR. OREN: Dr. winoker.

DR. WINOKER: I would also endorse the view that treating suicidal behavior in the context of schizophrenia or schizoaffective disorder is a recognizable and meaningful clinical phenomenon. And with the previous clarification that we're not necessarily confined to talking about specific diagnoses, I do think these are meaningful targets to look at efficacy data to evaluate.

DR. OREN: Dr. Malone.

DR. MALONE: Earlier you had spoken about pseudospecificity, and I think, if I understood the data from Dr. Meltzer, the schizoaffective population seemed to have had suicidal ideation at least 90 percent of the time --

DR. MELTZER: Yes.

DR. MALONE: -- and the schizophrenic 60

percent of the time. I don't know how that ties to suicide being part of the syndrome and that to pull out suicide would be one of those pseudospecific phenomena.

DR. LAUGHREN: But, again, what it comes down to, in part, is what the data show. If you have a symptom that's part of a syndrome that responds differentially, then that might be a setting where you would be willing to focus on a particular symptom. The concern, in general, about pseudospecificity is that it's an artificial narrowing of the claim, that you have a drug that works for a variety of symptoms of an illness, but you choose, for whatever reasons, to focus only on a few of them when, in fact, it has an effect on all of them. But if you have a situation such as this where you have a particularly troublesome symptom that's part of an illness that does not respond to other treatments for that general condition, but does respond to this treatment, that would be a setting where there would be some legitimate reason for celebrating that finding. I think that's the difference.

DR. OREN: Dr. Cook.

DR. COOK: So,to follow that, I was somewhat convinced that it seemed to be treating

suicidality independent of treating psychosis, which would be an important distinction here. I don't know if we're going to address right now whether we thought there was evidence in schizoaffective disorder, we're going to defer that because that I wasn't convinced about.

DR. OREN: We'll defer that for the moment. If I could just say this to either Dr. Katz or Dr. Laughren, perhaps to restate what you've already clearly stated, but just for the record, the fact that an approvable letter has already been issued for this, that indicates that in the sense of the FDA, this condition or this state of suicidality is a, in the Agency's opinion, serious enough or a consequential enough state that going down the slope, if you will, is a step potentially worth taking.

DR. KATZ: Well, right, but again I would just reiterate that the fact that we have sent an approvable letter really, other perhaps than in that very narrow sense, shouldn't be taken to -- we'd really sort of like you to put that out of your minds, if you can, and just sort of come to an independent view or give to us an independent recommendation. But, yeah, the approvable letter is what it is. We think that it's certainly a possibility, as Tom is

saying.

DR. OREN: Dr. Winoker.

DR. WINOKER: I wanted to follow up a little bit also on Dr. Cook's comment. A small piece of the data presentation that we haven't focused on much, or talked about, is that, overall, as I recall the data, there were comparable improvements in overall PANSS ratings for both groups, about 25 points, as I recall, in each case. So, we do have, on the face of it, evidence for both treatments being comparably effective for general traditional symptoms that are usually looked at in the treatment of schizophrenia but, still, the evidence which we can talk about further about the suicide behaviors.

DR. COOK: The problem I just realized is that we have different analyses, so if we look at how the PANSS data were presented, that's the same analysis and presentation that showed no differential effect of clozapine. So, it's very similar to the CGI data. So, we would need the PANSS data analyzed as a survival analysis, to be able to see that, in fact, when people were suicidal, they weren't having a worsening of their psychotic symptoms -- unless I missed that particular analysis.

DR. OREN: Dr. Ortiz.

DR. ORTIZ: I have a concern about the word "emergent" suicidal behavior because I think it implies an acuity, plus I think it also is suggestive of an impulsive suicidality that is more common, I think, with substance abuse or maybe borderline personality disorder.

DR. OREN: Dr.Katz.

DR. KATZ: I think it's a fair point. I think we use the word "emergent" in the sense of something that emerges. Maybe it's a wrong usage. I don't think we necessarily meant an acute event of the sort you're talking about. I mean, that can be specifics of the wording, although we've asked you to address that, I think can be discussed, but we didn't intend to have it mean that.

DR. OREN: Dr. Hamer.

DR. HAMER: I also wondered about the use of the word "emergent", although I didn't wonder about it in its context of an emergency, but in exactly the context of emerging, and that was that since the subjects for this clinical trial were chosen, in some sense, to be rich in suicide potential or in suicidality, then I'm not sure we should be reading the data in this trial as including suicidality that emerged during the trial. I mean, it was there when

they started. They were chosen for possession of it.

DR. KATZ: A little more clarification. Originally, I believe, the sponsor proposed language along the lines for the treatment of suicidality, and we were trying to make a distinction that these patients weren't, at the time of enrollment into the study, acutely suicidal. As you point out, they had a history of suicidal behavior or ideation in the past, but at the time of their enrollment we were not treating an acutely suicidal episode. So, we tried to make a distinction between treating suicide, which was what was originally proposed, which we felt that the study didn't look at, and preventing that sort of behavior in the future, even in patients who had a history of it. That was really, I think, the idea.

DR. OREN: Dr. Laughren.

DR. LAUGHREN: We're open to suggestions about how to articulate the claim, and that was one of my major questions. And in other areas where we look at maintenance trials -- for example, we have used language such as "delaying the time to a suicidal event" -- that may be an alternative way of -- so that you're not suggesting that it's new behavior, rather, you're delaying the time to an event that might be expected in a particular population.

DR. OREN: Is there anyone who might want to propose any kind of language -- not yet referring to diagnosis, but referring to sort of the target symptom or target state, that we might achieve consensus. Dr. Katz.

DR. KATZ: Can I suggest that we sort of leave the details of the wording until we've decided that it ought to be approved for something?

(Laughter.)

DR. OREN: Fair enough. Dr. Malone.

DR. MALONE: I juts wanted to ask a question, really. If schizoaffective disorder had a 90 percent rate of emerging suicidality, or whatever you wanted to call it, would -- the if you label this drug for suicidality, would it be the drug of choice then for schizoaffective disorder so that a physician might be derelict for not using it in a patient who had schizoaffective disorder?

DR. KATZ: Well, I don't think we're in a position to say what the drug of choice is for anything, but we would hopefully construct an indication that accurately reflected the data. So, I think it speaks to Matt's point about what ought the claim to be, even though it hasn't been shown to work in the traditional sense. In schizoaffective patients

you might decide that it has been shown to work to prevent suicidality, or however we choose to say it. So, we would hopefully accurately describe what the data showed, and how it's used is a separate question.

DR. OREN: Let me ask you, is there any consensus that just as a general target, suicidality, or however it would be referred to, is a good target for a claim?

DR. RYAN: Two thumbs up for suicidality.

DR. OREN: All right. Not yet focusing on specific language, the other part then of that first question was applying it towards schizophrenia or schizoaffective disorder. So, shall we turn then to the diagnostic of which group or groups might be supported.

DR. RYAN: Let me see if I can state the problem, but it's unlikely to be more helpful to you in clarifying thoughts than mine have been.

It seems like they proposed an analysis across schizophrenia and schizoaffective disorder, without being powered for separate analyses, that they have the indication for schizophrenia and not for schizoaffective disorder. We will discuss probably in a more spirited fashion subsequently, but at least in the first interpretation we had an overall p-value for

the study on their proposed outcome measure, which they picked rational basis, they got the p-value on that one, and that the subgroup analysis is relatively uninformative, which is in the schizoaffective it's not different from the schizophrenia, but it's also not different from the control treatment because it's sort of intermediate and so you don't have a significant difference either way, but they knew they weren't powered for it going in, and that's where my thinking stops, but are we sort of agreed on that part, or that's what you're seeing, Dr. Katz, on what they've presented?

DR. KATZ: Yes, I think generally that's true, although I don't remember the number of the slide, but you had the slide up with the point estimate of the effect, the difference within the treatments, or the hazard ratio, whatever it was, and the confidence intervals, and the estimate of the effect in the schizoaffective patients was, I'll say -- that's it.

(Slide)

Thank you -- was less than, or larger if you want -- it was less compelling a finding that schizophrenia by itself doesn't overlap with one, that was significant by itself, whereas the schizoaffective

was not significant. Now, again, I don't believe it was powered to look at the -- I don't believe it was powered, anyway -- to look at the individual diagnoses, but that's the data. So, the question, besides Matt's question which was is it a real entity or was it adequately defined in this study and did they capture the right patients who should be called schizoaffective, but is there a differential response. We have what we have.

DR. OREN: Dr. Hamer.

DR. HAMER: With the exception of Clozaril and some other medications, in many, if not most, of the clinical trials that I've either run or participated in designing or in one way or another for antipsychotics, almost all of those trials took in patients who had both diagnoses of schizophrenia and schizoaffective disorder. I don't think that we're being asked to do anything unusual in that sense. This trial was designed to have both schizophrenia and schizoaffective disorder, however ill we may define it as entry criteria, and in that group as a whole it showed an effect for whatever that's worth. Now, I have my own difficulty with the blinding issue, but I'm not at all astonished to see that it showed the effect overall and failed to demonstrate it in any of

the subgroups, except schizophrenia which comprised most of the subjects anyway.

DR. OREN: Dr. Katz.

DR. KATZ: It's true that other studies have looked at both populations, but we've never granted a claim for schizoaffective, we've limited the inference to only the schizophrenia population. So this is different in that sense because we're being asked to expand the inference to both types.

DR. HAMER: So that means that we're pretty much treating schizoaffective off-label?

DR. LAUGHREN: Well, of course, you have to keep in mind that you would also be treating non-treatment-resistant schizophrenia off-label because the Clozaril only has a claim for treatment-resistent schizophrenias.

DR. OREN: Dr. Mehta.

DR. MEHTA: This protocol was discussed by the FDA and the sponsor four years ago. I guess the protocol said it very clearly, that these other two different diagnoses which were going to be used. One cannot use a post-trial argument that one of the subsets is not significant because if you look at the last slide, you can't recommend a drug for males or even females because none of them is significant

individually.

So, you can't change the rules of the game after you already agreed four or five years in advance, and that's a concern I had.

DR. OREN: Whatever the rules are, I think it's the duty of this committee as independent outside experts, one hopes to give our best opinion regardless of what took place previously.

DR. COOK: I would add, the question isn't whether this means the overall trial was positive or negative, which is probably what was decided years ago. I doubt years ago the idea would be this would support a new claim for schizoaffective disorder, it's two different issues.

DR. OREN: So, if there was to be some kind of claim referring specifically to schizophrenia and schizoaffective disorder, is there comfort or discomfort with a dual-diagnosis claim, or two-diagnosis claim?

Dr. Meltzer, I'll let Novartis answer, and then we'll come back just to the committee, but you can give the last word on behalf of Novartis.

DR. MELTZER: Well, I've seen a number of very large datasets from community mental health centers around the country, and the diagnosis of

schizoaffective disorder is about 25 percent of the sample. And I think it's very fortuitous, in a sense, that we didn't use a structured interview because I would bet, on average, the way the clinicians made their clinical diagnoses are comparable to the way it's done in America.

And what is happening is that when we completely rule out bipolar disorder by history and symptoms, you have this group of psychotic patients with a schizophrenic positive symptom/negative symptom type syndrome, and when, in addition to that, there is clearcut mood symptoms present, regardless of the temporal issue -- and that's where DSM4 came in and that's what most people don't understand that DSM4 diagnoses schizoaffective disorder in terms of a temporal relationship -- but the average clinician does, and this is why concomitant therapy is so prevalent today. Whenever they see depression, whenever they see mania, in addition to the schizophrenia picture, in the absence of reasons to call it bipolar disorder, they will diagnose it schizoaffective disorder.

And if they remember the RDC, the research diagnostic criteria, then we might call it schizoaffective manic or schizoaffective depressed --

in that finer RDC criteria it was beautifully laid out, and if DSM had stayed with it, we wouldn't be in this problem. But, clinically, I think it's very fascinating that in order to get this study -- or when sites were recruiting for this, one found about, what, 30 to 40 percent of the sample were considered schizoaffective, and the reason for that is just what I said, that's the population that's really at greatest risk for suicidality. And I would be concerned, really, if you did approve it just for schizophrenia, that it might be interpreted or might create some barriers to access to clozapine for the group that needs it perhaps the most -- that is, these people who the average clinician out there is calling, by his own empiric criteria, schizoaffective disorder.

DR. RUDORFER: I certainly agree that there's a major problem in the field in terms of identifying this disorder. However, I think we're faced with a dilemma that the inclusion criteria here with DSM4 definition, and I don't know how we could evaluate a claim where it's every clinician decides for his or herself.

According to DSM4, one needs a full mood syndrome, you need a full major depressive episode or a full manic episode, concurrent with criteria in (a)

for schizophrenia, for the diagnosis of schizoaffective disorder. Now, that means criterion (a) only calls for a month of psychotic symptoms. If people meet the full six-month criterion for schizophrenia, they should be called schizophrenia. If they are called schizoaffective by DSM4, it means they don't meet full criteria for schizophrenia. I mean, that's what we have to work with here.

DR. OREN: I'll recognize Dr. Leber, from the public.

DR. LEBER: This is a clarifying question I'll direct to Tom. In 1998, when this protocol was being planned, was it not the policy of the Division to make the claim for drugs used in the management of schizophrenia, antipsychotic rather than antischizophrenic and, if so, would that not explain the apparent dilemma that exists now?

DR. LAUGHREN: Yes, it's true. There has been a transition over the past four to five years. Prior to that time, all the antipsychotics did have a general claim, and it's since then that we've gradually shifted to focusing on schizophrenia.

DR. OREN: Dr. Kane.

DR. KANE: John Kane, Zucker Hillside Hospital. Just on this issue and keeping in mind the

nature of the patient population, if we think back to the demographic and treatment history characteristics of the sample included, these people had been ill for over ten years, and the average patient had made suicide attempts, was hospitalized for suicide.

I think we want to keep in mind the way that this drug is going to be helpful to patients who may need it. And I certainly understand the discussion here, and I think the point is well taken, that we've seen an evolution, but let's not lose sight of the population that really needs to be treated with this drug.

DR. OREN: Dr. Katz.

DR. KATZ: I think it is, of course, important to think about what is the population that might benefit from the drug or, in fact, might be treated with the drug, but we have to be concerned with what the data are and whether or not the population whom we're contemplating approving it actually was the population that was studied or is currently considered to be the population that we would indicate it for. So, we have to think about who it is going to be used in, but we really have to focus on what the data support.

DR. OREN: So, canvassing the committee,

is there any consensus on this diagnostic question? Dr. Cook.

DR. COOK: The only thing I'd like to state is we have a specific question, but often you're looking for more general direction. It seems to me that if this is schizophrenia or schizoaffective language on the basis of practicality, then that probably applies to every other schizophrenia indication, if most of them had put in similar sorts of populations. I don't think it's a particularly unique population, it's an appropriate population. Essentially, if you don't want this to be off-label for schizoaffective, that applies to the other antipsychotics. So, I just think it's a bigger policy decision than this specific study.

DR. LAUGHREN: Just one clarification. Again, if you recommended approving this claim, the claim is focused specifically on suicidality in these two populations, it would not be a general claim for either all schizophrenia or all schizoaffective disorder.

DR. COOK: I understand that about the specific language here, but if you extrapolate that logic, the same could be applied to the treatment of psychosis in schizophrenia and schizoaffective

disorder. I'm willing to say there's an independence here, and this is an interesting specific question, an important specific question, but as soon as you say this should be schizophrenia or schizoaffective disorder, the logic of extending that to treatment of positive symptoms in schizophrenia by antipsychotics would follow.

DR. OREN: Dr. Ryan.

DR. RYAN: Could I get a clarification from Dr. Laughren about the design of the study because it seems like you use the word "two populations", and yet that doesn't -- I'm having trouble making sense of that because when you approved it without power to test it in either one, it seems to me like it's possible you're thinking this is one population because if you're thinking about it as two populations and the study design leaves you in the quandary that we may or may not find ourselves in right now and -- you know, if you look at most of the other ways of saying whether is this one population we have trouble drawing the boundary versus two populations. So, what was the original thinking?

DR. LAUGHREN: Well, the focus is on suicidality. I mean, that's the primary focus of the study -- suicidality coming out of several different

populations. I mean, I don't know that I can be any clearer than that. And, again, I don't think this is so unusual.

DR. RYAN: But you didn't let them test it in bipolar disorder, say, or other things where it might be a completely splendid drug to treat the suicidality as well as the disorder.

DR. KATZ: Well, I think we're willing to grant a claim, assuming everything else is acceptable, for suicidality in schizophrenia and schizoaffective disorder. I think we would be willing to do that. The question has been raised that maybe these people didn't have schizoaffective disorder, as currently diagnosed, and therefore that would lead to misbranding, if you will, by saying these patients had schizoaffective disorder when, in fact, by common understanding they don't. So, that's one issue. The question is whether or not those patients really are labeled, if you will, appropriately in the context of the year 2002, or whatever year this is.

The other -- that's the main point, whether or not we really are dealing with the right population.

DR. OREN: Dr. Hamer.

DR. HAMER: Perhaps I'm wrong, but my

understanding of the way the diagnostic criteria were used here would imply that if these patients were mislabeled because they didn't meet criteria for a full-blown mood episode, then they probably met criteria -- the way that the criteria were used here, then they probably met criteria for schizophrenia. So, it's not like we have a mixture of schizophrenics and people who could be anything -- personality disorders, attention deficit disorder, whatever else -- it's either schizophrenia and schizoaffective disorder, or primarily schizophrenia. That's at least my impression of the way the diagnostic criteria were used.

DR. OREN: Dr. Ortiz.

DR. ORTIZ: Yes, I think I would agree with that. It sounds like the clinical information that we've gotten, that many of these people could have been schizophrenia and major depression, not necessarily schizoaffective.

DR. OREN: Dr. Rudorfer.

DR. RUDORFER: Or bipolar disorder with psychosis. I mean, I think the general issue -- one general issue I'm having problems with again is the fact that without the structured interview, we really don't know how the diagnostic criteria were used

because it sounds as if other than people being aware that there was a set of DSM4 criteria, we have no information on how the clinical data were applied to those criteria.

DR. OREN: Dr. Katz.

DR. KATZ: The other point when considering whether -- what populations it ought to be approved for, has to do with something that Dr. Mehta said, which was it wasn't powered to look at the individual subtypes, and there are many other demographic characteristics which we ordinarily wouldn't say, well, it doesn't work in men, or it works in women, that sort of thing. But you are allowed to look at the data as it was generated and, for example, if it turns out that the study was overall positive but all the action was in one particular subgroup and there was absolutely nothing going on in, let's say, the schizoaffective group, you could reasonably -- I mean, it's not immediately obvious what the best thing to do in that case was -- but you could reasonably say, well, yes, it was overall positive when we enrolled all these patients, but really it had no effect in one particular subtype. And, again, you saw the point estimate and the confidence intervals around the treatment effect for

the two subtypes. So, one could ask the question whether or not, even though these patients were, for example, accurately diagnosed and accurately labeled and the prospective analysis included all patients and it was overall positive, when you look at it there's nothing going on in one particular subset. I'm not arguing that position, but I'm saying that one could look at the data in that way.

DR. OREN: Do we feel the data for the schizoaffective population is strong enough for such a claim on the basis of what's been presented? I'm not hearing any disagreement on the schizophrenia side of the question. Dr. Hamer.

DR. HAMER: Well, looking at that slide which you've kindly flashed a couple of times, with all the effect sizes for all the various subgroups --

DR. OREN: Would you mind putting that slide up again, No. 39?

(Slide)

DR. HAMER: As I look at that pattern of confidence intervals and I see them -- all the point estimates hanging around there on the low side of 1 -- it seems to me that if we were going to deny schizoaffective disorder which was a relatively smaller subgroup, then we might want to deny a variety

of other of these claims, too -- like whites, it doesn't seem to work too well in whites, or elderly people over 44 -- I guess I'm in that category --

(Laughter.)

So, I have a hard time singling out schizoaffective disorder and saying, yeah, it doesn't work in that subgroup.

DR. OREN: Any other comments on that?

(No response.)

Okay. We're also asked to talk about expanding -- I'm sorry. Dr. Katz.

DR. KATZ: I'm just not sure what the sense of the group is on this question about whether or not schizoaffective ought to be included in any potential indication.

DR. OREN: It's sounding to me like there is -- maybe by virtue of silence, so I'll ask people to speak up -- but it's sounding to me like the group is, on the whole, supportive of such -- no? Would it be worth -- should we go around and just invite people to comment? You can pass, as well. Dr. Mehta.

DR. MEHTA: I would include both indications as part of the protocol.

DR. OREN: Dr. Malone.

DR. MALONE: I'm not on the vote --

DR. OREN: This is just discussion.

DR. MALONE: I don't know. I think it a bit strange to have a disorder indicated for suicide, but it's not already primarily indicated for the main treatment. So, for instance, Clozaril has schizophrenia as an indication, but --

DR. LAUGHREN: Can I just clarify, it does not have a broad claim for schizophrenia, it has a claim for treatment-resistant schizophrenia, which is -- you know, it's a fraction of that population. So, we would be moving into both areas, not just into schizoaffective. We'd be moving into suicidality in garden-variety schizophrenics as opposed to treatment-resistant. So, it's really two new populations.

DR. MALONE: And this is apart from whether there is evidence to say that it actually does treat suicidality? But apart from that, I don't really see any big problem with including schizoaffective if they were part of the study population. If you think it worked in the study population, I don't think you would take schizoaffective out of the study population.

DR. OREN: Do you think it worked in the group?

DR. MALONE: Well, see, the way the study

was designed, you just have two active comparatives, and I'm still not convinced that just having the two active comparatives shows that the one drug, just because it looks better than the other, is shown to be an effective treatment for suicidality. So, that's why I say if you assume that, I wouldn't have a problem with including schizoaffective.

DR. OREN: We're talking prevention rather than treatment.

DR. KATZ: Yeah. You know, in some sense, we're doing this backwards because we're trying to figure out in which population the finding has occurred, when we haven't really signed off on the fact that there's a finding in the first place. So, I think part of this we can do sort of backwards. We're trying to figure out who the patients were, that sort of thing, I think you can do that independent of what the results were actually, to some extent, so I think it's probably okay. But I don't think we've yet fully discussed the question about whether or not, with all the potential problems -- blinding and everything else -- the study is really a bona fide positive study.

So, I think if we could just figure out which patients a particular claim would include,

before we figure out whether the claim is valid yet, is doable. I don't think we're yet at the question of does it work.

DR. OREN: Dr. Laughren.

DR. LAUGHREN: Let me try and clarify what I think two separate concerns of the committee are. One is when you look at the data for the schizophrenic patients as opposed the schizoaffective patients, you see a somewhat different effect size. This is a common subgroup problem that we deal with all the time. So, I think that's one issue, is how you evaluate those data.

But a separate issue the one that Matt brought up, and that is the question of whether or not, in thinking about schizoaffective, the patients in this particular trial were accurately diagnosed. There seems to be an acceptance of the current criteria for schizoaffective illness, the question that seems to be on the table is whether or not, in this particular study, they were accurately captured.

DR. OREN: Dr. Wang.

DR. WANG: I think in terms of clozapine looking like it's effective in the schizoaffective population -- I mean, the point estimate looks like it's trying to be, and it's probably under-powered.

I think my concern would be since we're not seeing data on its treatment of psychosis in that population, maybe some kind of sub-analysis just to show that PANSS scores weren't horrible specifically the schizoaffective population.

If the treatment of psychosis was basically the same as it was in the schizophrenia population, that would reassure me because that speaks to this expansion of use not only to treat suicidality, but also psychosis in schizoaffective population.

DR. OREN: Does Novartis have any data on that specific question?

DR. ZANINELLI: Not at the moment, no.

DR. OREN: Okay. Dr. Ortiz.

DR. ORTIZ: Do you want us to check in on this? I think Dr. Laughren brought up what my main concern is, that there were not consistent criteria used for the diagnosis of schizoaffective disorder, and on top of that we have international confusion as to what schizoaffective disorder is. So, therefore, I would not be in support of the schizoaffective label.

DR. OREN: Ms. Bronstein.

MS. BRONSTEIN: I'm going to pass on this.

I see it as a diagnostic question, and I don't feel qualified.

DR. OREN: Dr. Ryan.

DR. RYAN: Sure, I'm near equipoise, but not at it on balance. I'd suggest not including the schizoaffective labeling because of the issues that Dr. Rudorfer brought up and that Dr. Laughren elucidated, that it's substantially likely that a number of those were schizophrenia, and there may have been a very small number of schizoaffective people that it was tested in, making it just hard to get a separate estimate.

DR. OREN: Dr. Rudorfer.

DR. RUDORFER: Well, I'd just like to emphasize one additional point -- that is, it is very possible, as I understand the current evidence, that a subtype of schizoaffective disorder is closer to mood disorder, specifically to bipolar disorder.

Clozaril may or may not have the same effect there as in the subtype of schizoaffective disorder, it's more like schizophrenia. My overall concern is that we simply don't know because we don't have those data, we don't have the subtype analysis.

And if I could add one other caveat, throughout we've made references to the fact that

suicidality often is, in fact, a component of mood disorder. We heard that we don't have data on whether people had, say, frank depressive episodes in the context of this two-year study, but people were being treated with concurrent medications along the way, so I have a lot of trouble still teasing out a lot of pieces of this puzzle. For instance, could a person that developed a secondary depression along the way, maybe with suicidality as part of that, and they are treated with -- even the Clozaril people, we were told, were often treated with other medications -- and they are treated with something else for that secondary mood disorder, the suicidality improves and they go on and, for all we know, the Clozaril or the Zyprexa had nothing to do with change in the suicidality status. I think there are simply too many variables at play.

DR. OREN: Dr. Winoker.

DR. WINOKER: We were told this morning, if I recall, that the diagnoses were made using DSM4 criteria, and I think the main problem that has us hung up now is the lack of use of structured clinical interview as a basis to obtain data to apply diagnosis.

I don't know whether the sponsor has any

additional comments that they'd be in a position to make in terms of the extent to which the fidelity of diagnoses based on the quality of clinical information was obtained, that baseline evaluations would support the diagnoses.

If we could feel confident based on understanding the relationship between the information from baseline clinical evaluation and the assessment of diagnostic interview, we might be more comfortable coming to the kind of position that you're asking for.

DR. OREN: Dr. Krishnan, do you want to address this point?

DR. KRISHNAN: Yes, just very briefly. I think Matt's point is could this be bipolar disorder. If it was, then we clearly would have missed it if we had not read through every chart that we had seen. Of the 400-some patients, 577 events, we saw the charts. We reviewed those charts. They are not bipolar disorder.

There's another piece of evidence which I think points it out. Look at the AA experience. If it's a bipolar population, would you not expect hypomania (phonetic). That was not an event profile that came up.

So, this, from my opinion, is not bipolar

disorder. Whether it's schizophrenia and how much you extend it to schizoaffective is another question that I can't answer, but it's not that. If you look at the mood event rate, the depression event rate is different, but not mania, no hypomania. So even if you take this through 8 mood disorder patients, that doesn't again suggest that the majority of this population, or even a significant proportion of this population, is bipolar disorder. I hope that helps. Thank you.

DR. RYAN: Were they schizoaffective, though, when you reviewed them?

DR. KRISHNAN: In the broad category, yes, mostly schizoaffective depressed. I don't recall except one or two where there was any schizoaffective mania features in it. When you read through the case histories, remember, even if it is not a diagnostic interview -- and I actually think in long-term patients, case histories are more important. In many ways, the psychotic patient coming in trying to get a SCHD interview is not the most reliable thing. What is often more reliable is if you have the full background information to take a look at, and I think that's what we had in this case. Thank you.

DR. OREN: Dr. Meltzer.

DR. MELTZER: I happen to have the DSM criteria for schizoaffective disorder on my laptop, from a lecture I gave about six months ago, looking at the relationship between the three disorders, and I'll spare you the lecture, unless you want to know my bottom line on it, but it's very interesting to look at the criteria as they really are written.

Lead criteria, as Matt said, they have to meet criteria for major depression, mania, or mixed-episode concurrent with the Class A criteria for schizophrenia, namely, delusions, prominent hallucinations, incoherence, and catatonic behavior.

Now, the next one is the kicker. The next one says, "Delusions or hallucinations for two weeks, without prominent mood symptoms". And this is what nobody pays attention to. So, I'd be very surprised if that were in the thinking that led to the clinical diagnoses.

What is prominent is the next criterion -- "Mood symptoms prominent for substantial period of time psychosis is present". That is what the clinician operations on. That is the operational definition for him. When they see the Criteria A for schizophrenia and mood symptoms are prominent, they call them schizoaffective. And because of the link

that I showed you between depression ratings and suicidality, a lot of the very people that are going to have the kind of histories that went into this are going to be diagnosed by the community psychiatrist -- not your GPs -- as schizoaffective, and I think you need to take that into consideration when you make your final decision. I mean, I'd have to say it's probably true that, according to DSM4 criteria, that independent period of psychosis with no mood symptoms, we can't really say that there was that prominent a group of DSM4 schizoaffectives.

What the world, on an operational basis, calls schizoaffective disorder, they were studied, and they showed a differential effect of the two drugs.

DR. OREN: Dr. Winoker, do you want to add anything else?

DR. WINOKER: Those were helpful, but I'm not sure I got an exact response to my question, which was, in the absence of using a structured clinical interview, were other steps taken to verify the diagnosis, for example, by reviewing the initial clinical history and seeing that there was an appropriate support for the diagnosis through the specific intake history that was obtained.

DR. COX: There was a diagnostic worksheet

which was basically a checklist straight out of DSM that they had to check off, but there was not formal interview, but they did have to check off and the PI had to sign off on the diagnosis using the checklist, and it was basically just DSM4 criteria.

DR. WINOKER: So the checklist was geared to identifying the presence of symptoms that led them to establishing the diagnosis?

DR. COX: That's correct.

DR. OREN: Dr. Hamer.

DR. HAMER: The lack of a structured clinical interview doesn't bother me very much. Rarely have I seen my colleagues use structured clinical interviews in their ordinary day-to-day clinical practice. So, the people who are going to be using this medication in their patients won't, by and large, be making diagnoses with structured clinical interviews.

Except for my continued discomfort with the blinding issue, I'm comfortable in the claim for the schizophrenia and schizoaffective disorder for suicidality, generally.

DR. OREN: I'm curious whether your discomfort is outweighed by your support for the claim, or not?

DR. HAMER: You know, I don't know. I honestly believe -- and I've come to this belief during the course of this meeting as opposed to based on the material in the briefing books that I red beforehand.

I've increasingly come to believe that it would have been possible to have designed this as a virtually double-blind trial where the only people who were unblinded was the psychiatrist who actually prescribed the medication, that some psychiatrist had to know what the medication was the patient was on, and the technician in the lab who either stuck or didn't stick the patient with the needle, that everyone else in the entire study could have been blinded, the patient goes into the lab, either gets stuck or doesn't get stuck, and then the patient just has to get told "Tell your doctor whether you got stuck or not".

So, the fact that this wasn't designed this way weakens the strength of the evidence, although it's hard to see how it could have introduced the systematic bias, but then again we usually like blinding whether we can see how lack of it would introduce a systematic bias anyway. So, that's my discomfort.

My discomfort is more based on the regret that this study was not designed in a much more blinded manner.

DR. OREN: Dr. Wang, do you want to comment?

DR. WANG: Yes, just on the schizoaffective issue. Again, it would be nice if there were some reassuring data just either from InterSePT or another RCT, just to suggest that clozapine is effective for psychosis in schizoaffective disorder because the last thing you want to be doing is treating someone's suicidality and then potentially give them an ineffective antipsychotic. If there is that data -- and maybe there is -- then I would feel comfortable expanding the indication to also then include suicidality.

DR. MELTZER: There are those data, published data, from a paper by Joe Calabrese and myself, of treatment-resistant bipolar disorder and schizoaffective disorder, structured interviews, DSM3 or 4 criteria -- I'm not quite sure, probably 4 -- and the drug is more effective in bipolar disorder -- strikingly effective in these treatment-resistant disorders -- but it was also effective in the schizoaffective disorders. That's in treatment-

resistant schizoaffective, and I've analyzed my own data on schizoaffective versus schizophrenia, and in that population the effect on psychosis and mood symptoms is greater in schizoaffective disorder than schizophrenia. That's also published.

DR. OREN: Dr. Cook.

DR. COOK: I also have concerns about the blinding, but on the question of schizophrenia or schizoaffective, I'm very much in the middle, slightly to it's okay. It's almost as much an abstention as anything.

DR. OREN: Personally, I think the schizoaffective disorder is a second level of leaping. I think claims need to mean something, and certainly I think it's much stronger, the claim focusing on suicidality in schizophrenia, and I would be quite comfortable with that claim. To go beyond it, I'm glad it's on somebody else's shoulders to make that additional decision.

Let's move on. On the subject of leaping, as has been brought up, one aspect of this is expansion of the Clozaril beyond treatment-resistant schizophrenia, specifically to schizophrenia in general, and perhaps beyond that. How do -- do people want to offer any comments just in general on the

expansion of the claim? Dr. Wang?

DR. WANG: It seems like there's two ways you could expand it. One is to expand it to all patients who are at high-risk of suicidality, regardless of whether they're treatment-resistant or not. And then a second way to expand it is just to patients who are treatment-sensitive, whether or not they're at high risk for suicide. I mean, there are two sort of separate ways to expand it. The first depends on what the --

DR. RYAN: My apologies. I didn't understand the second point at all.

DR. WANG: You could also expand it just to treatment-sensitive patients, capture everybody. In other words, not designate necessarily for high risk. And there's a reason why I'm bringing this up. The first one, if you remember what I said, it seems supported by at least the back-of-the-envelop calculation that Dr. Kane showed where if you sort of weigh the risks and the benefits of potentially expanding into this high-risk population of treatment-sensitive and treatment-resistant, it looks like it's in favor, maybe an order of magnitude in favor, of clozapine. In other words, the risks that you add for agranulocytosis are relatively minimal, and same for

cardiomyopathy.

The second question is much trickier. It's not an obvious win for the sponsor. It would take a decision analysis of some sort. The reason why I'm raising this is because it's hard to identify patients at high risk for suicidality. And so in the real world, the real practicing clinician, it's going to be a mixture of the two. They will not necessarily be able to identify their patients who are at high risk for suicide both because there are very few predictors -- even from the InterSePT study, there are only two significant ones -- and the relationship is so weak -- again, from the InterSePT trial, the point estimates for the other co-variates -- even for prior attempts, it was about a 3 percent increase per attempt. So, in reality, the clinician in the real world will end up having to apply clozapine to a larger than just high-risk population. So, that's why I'm raising these two potential scenarios as ways to expand the indication. I hope I didn't lose everyone there.

DR. OREN: Dr. Ryan.

DR. RYAN: I'll try. I think I understand what you're saying, but I'm not sure, so let me go through it again and see if I can repeat it, or at

least explain my confusion.

You could, in theory, say apply the algorithm that was applied in this study to select your patients. Given that, you prevent somebody's suicide attempt on an 87 per 1,000, by treating with the Clozaril rather than a different compound -- and we'll talk later which different compounds.

Obviously, you could say that one could neither apply that reliably, or people will generalize too much and sprinkle it higgely-piggely on people, but it seems like they gave a number in here which is fair enough -- you know, it's your best estimate so far, 87 per 1,000 people that you treat with Clozaril rather than something else, but prevent one or moire suicide attempts, and they gave some dollar value to be imputed value of preventing a suicide attempt.

DR. WANG: Just to clarify, in this material, the question that was put to us is could you expand the indication to treatment-sensitive and treatment-resistant patients who are at high risk for suicide, and that's what I was calling point one, the scenario one. And to answer that question exactly as Dr. Kane did, you weigh the risks versus the benefits. And at least if you do that back-of-the-envelop calculation, which didn't take into account

potentially greater efficacy of clozapine, that sort of thing, it looks like a pretty clear win for clozapine.

I'm just saying there's another way in which the indication might, in the real world, de facto, get expanded, and that is you may not be able to target patients who are at high risk for suicide, you may end up having it be given to a broader population that is essentially a treatment-sensitive and treatment-resistant population maybe not necessarily at high risk for suicide.

DR. COOK: In your logic, the one thing that -- I wasn't worried about the second -- is the fact that there's not a correlation -- there aren't predictors -- may have been because they were good at selecting the specific groups. They didn't study the larger group you're talking about, and I think it would be important in labeling to make that clear, what the trial was about. It wasn't the overall population -- that's your concern -- is to highlight for people that this was a selected group of patients.

DR. OREN: Dr. Katz.

DR. KATZ: We asked the question in a certain way, but I think it is fair to ask whether or not the claim that we are contemplating is in any

sense practical. We can always fashion a claim that conforms point-by-point to the study that was done, but if it turns out that that's clinically meaningless or misleading or along those lines, we'd like to hear it. I don't know if people think it is, but that would be an important thing for people to talk about.

DR. OREN: Dr. Winoker.

DR. WINOKER: This study was conducted with a majority of patients who were viewed as -- who were entered because of suicidal behavior that got them in, the majority of whom were not treatment-refractory, so the data that we're looking at was based to a large extent on people that from a clinical perspective showed suicidal behavior at risk, but didn't fit into the treatment-refractory subset. If, at the end of the day, we end up as a group feeling convinced by the data for differential significant beneficial effects for Clozaril for suicidal behavior potential in this population, I think that logically extends the indication beyond the treatment-refractory group because we don't currently have specific treatments to recommend, and we have apparently a situation where a comparative antipsychotic drug that was effective in general for symptoms of psychosis showed less beneficial effects for suicidal behavior

specifically.

DR. OREN: Dr. Katz, could you clarify what kind of a label or what kind of a claim might be made that would be impractical?

DR. KATZ: Well, for example, we defined -- the protocol defined treatment, you know, high risk for suicide in a certain operational way, and these patients presumably met those criteria. But if it turns out, as Dr. Wang points out, that that's a diagnosis that, for all intents and purposes, can't be made practically on a clinical basis by the average practicing psychiatrist, that would put us in a tough spot, but we'd like to know. If that really is true, we'd like to know. I'm certainly not saying it is true, but it's been brought up, and it's not an unreasonable point to raise.

DR. MELTZER: Can I please speak to that issue because there really is enormous literature on that. I've reviewed it a number of times, contributed to it, and it's really in high agreement, enormous agreement, the risk factors for suicide and schizophrenia. And the proof of it is that how many events we had in this study. We used those criteria to design this study, and the No. 1 criteria is having made a previous suicide attempt. That probably

accounts for 50 percent of the variants.

Then you get into substance abuse -- male, first decade of illness, family history of suicide, depression, hopelessness -- what isn't a predictor is control of positive symptoms, which is why the other extension that you postulated would not be in the patient's best interest at all.

So, is it possible for the average clinician? Absolutely, to determine who is at high risk. Now, can they miss a lot of people? Absolutely, the people who -- and a good example is, in fact, what happens in the FDA database where low risk of suicide is supposedly one of the criteria for entry into the study, yet in the literature that was reviewed by the FDA and by Kahn, the rate of suicide in that group was no less than what is average for the population. So, you can't very well rule out or identify the low-risk patient, but you can certainly identify the high-risk patient, which is what the basis of the claim is.

DR. OREN: Dr. Malone.

DR. MALONE: You know, I think if you look at the number of patients screened for the study overall versus the number enrolled, a very high percent -- 80 or 90 percent of the people screened

were enrolled in the study -- so I guess when you're screening, you're trying to rule out people who don't meet your protocol. So, if that high of a rate of screening to enroll occurred, I would think a similar rate would look -- you would see a similar rate when you had a commission that's trying to judge whether this patient indeed meets criteria for anything you write, especially if you're writing something about at high risk for suicide.

DR. OREN: Dr. Laughren.

DR. LAUGHREN: I think the company can probably speak to that. The question is what was the source of patients referred for screening. I'm assuming it was not just a random sample of the population of patients.

DR. KANE: I would make two points. The fact that the screening rate was so high means that the subject were prescreened, and clearly there are such patients out there, which is one of the things we've been emphasizing, and the sites were able to identify them reasonably well. But these were not just random patients taken from clinics or hospitals, these are patients who were identified as potentially eligible for the study by the clinicians who knew them.

DR. ZANINELLI: Just to emphasize that point, remember that the design phase before the study start was about a year, and potential sites were lining up patients for the study start. So these were preselected, as Dr. Kane said.

DR. OREN: Dr. Malone.

DR. MALONE: Just a comment. When we do a study in aggression, we prescreen everybody for them to come in because we don't want to go through a whole interview. And only people in the study are prescreening, yet our enrollment rate based on just them meeting the criteria for the study still falls around 50 percent after a first screening that we've done before we bring them in for more detailed screening.

DR. KANE: John Kane, Zucker Hillside Hospital. You have to keep in mind that this was events that in many ways affected this trial. We took patients who were substance abusers. We took patients who had co-morbid conditions. We took patients who required concomitant medication. The average clinical trial is much more exclusive and, in fact, excludes people with risk of suicide. So, I think that, coupled with the fact that, as Dr. Zaninelli said, there was a lot of advanced warning, people were eager

to participate with the anxiety that I mentioned, but they certainly felt that this was an important opportunity, and they had many patients that they felt would be eligible.

DR. OREN: Dr. Malone.

DR. MALONE: Just to followup, usually when we're excluding people out, it's only because they don't meet symptom criteria, not because they have other exclusionary diagnoses. So, usually they, on the phone, seem to meet a certain criteria for aggression to get in the study, but when you bring them in, it's really the aggression criteria they don't meet -- the specific symptoms, not that they're excluded for other reasons.

DR. OREN: Do you have a direct answer --

DR. COX: I don't have a direct answer to that question, but I just wanted to add, one of the reasons that the enrollment rate was so high is that we responded with a randomization number within 30 minutes of the site's request because we considered these patients to be in a critical state, or potentially. So, there was only a 30-minute time period. So these patients were generally screened and randomized in a very short period of time. So there wasn't a lot of time for patients to change their

mind.

DR. OREN: Other comments from the Panel specifically on expansion beyond the claim for treatment-resistant schizophrenia? Dr. Laughren.

DR. LAUGHREN: Can I raise sort of a related question to expansion of the claim? My question has to do with once a patient is designated as a high-risk patient -- perhaps a treatment-sensitive patient, but a high-risk patient for suicide -- how long does that status prevail? My question is, supposing you have such a patient, you treat them with Clozaril, they are improved, they are stable for some number of years. Do they stay on Clozaril forever, or is there some point at which -- again, this is a patient who is not treatment-resistant, they are just high-risk -- is there some point at which they revert to a non-high risk status and can go back on something else, or once that decision is made are they on Clozaril for life?

DR. MELTZER: That's a terrific question, and there are no hard data to answer it. I can give you a number of anecdotes that the answer for some people is for life. I have seen people have a phenomenal response to Clozaril in terms of people with multiple suicide attempts, and go into long

periods of remission that no one ever expected they would on Clozaril. Clozaril is stopped for one reason or another, and the suicidality comes right back.

Now, I can also imagine -- and that's anecdotal data, but I can share them wiht you if you want -- but I can also imagine that there are certain constructs here that are relevant, like the issue of hopelessness which stems from social and work function -- that is, people really work out some of the fundamental problems they've had. And we heard from the NAMI person who spoke, there really are a number of major recoveries, that as people recover, some of them, the urge to take their lives might diminish sufficiently, they could be transferred to some other medication. But those are going to be some real problems out there. There's no real simple answer. So, it might well be -- I mean, I'm speaking now as a clinician, I would be very loathe to take somebody of the kind that I just mentioned to you, with recurrent suicidality, got on clozapine, did well, and never recommended they stop it because there was something else that seemed to appeal to them for some other reason.

DR. KANE: John Kane, Zucker Hillside Hospital. If I could add to that, the database that's

most informative in that regard is the Walker database, where the three groups that were examined included patients who had been on clozapine and patients who came off clozapine. So, that would suggest that discontinuing clozapine in a high-risk population does increase the risk of suicidal behavior.

DR. OREN: Anything else on this?

(No response.)

Just a little bit off the top, but we've been focusing on clozapine, but the study obviously studied olanzapine, and we've been asked to make some comments on the interpretation of the InterSePT study with regard to olanzapine. I think, Dr. Malone, you made a comment about that before. I don't know if you want to say anymore.

DR. MALONE: No. I think I said that it looked like Clozaril worked better than olanzapine in the study, but I don't know that you can say anything else.

DR. OREN: Dr. Katz.

DR. KATZ: At this point, I think I would sort of argue that we ought to attack the primary question because before we start getting into how we're going to describe it in relation to olanzapine,

I think we really have to figure out whether or not we think this trial, as conducted, with the results that we've seen, can actually be considered sufficient for approval. And I think when we address that -- when you address that question, I think we also really do have to finally take on the question of whether or not a single perspective control trial meets the current criteria for approval on the basis of a single trial and what's called confirmatory evidence. There's no real -- I mean, just to give you a context for that, as Tom pointed out, in '97 the law was changed to say that that can be a standard for substantial evidence of effectiveness -- single trial and confirmatory evidence. But Congress, in its wisdom, didn't see fit to define when that standard ought to be applied, or what confirmatory evidence means.

The Agency has constructed a guidance or a document which talks about the circumstances in which a single trial and confirmatory evidence might be acceptable, and Tom pointed out some of that in his opening remarks. It's typically a case where -- although there's nothing hard and fast -- but, typically, it's a case where the study shows an effect on mortality or some irreversible morbidity and really can't be repeated on ethical grounds. Typically, such

a study would show, as Tom pointed out, internal replication across individual sites, or show, in effect, in multiple different subgroups, severe patients, mild patients, moderate patients. It might have a very low p-value, suggesting that it wasn't positive by chance alone, it was very unlikely -- more unlikely than the typical standard we ordinarily apply -- to be positive by chance alone.

So, those are sorts of the types of things that we would consider, or typically a thought that would apply in this case. So, I think the committee has to think about whether or not a single trial of this sort that we have in front of us, where there are questions about blinding, about the outcome, about the robustness of the finding -- the overall p-value is .031, I think, or .03 -- so when that's all put together, does that constitute the sort of evidence to which we can apply the one study plus confirmatory evidence standard. I'll stop there.

DR. OREN: The question is, does this one study show something -- we haven't necessarily agreed what that something is, but putting that aside, what do people think, does the study show something sufficient that the FDA can stand on in approving a claim? Dr. Malone.

DR. MALONE: As I understand it, it's one well-controlled study and, to me, if you have a lot of questions about a study, you might argue that it's not a well-controlled, or that there's some problem with it, and that you wouldn't want to go on the basis of that one study.

There is some confirmatory evidence, but I think you would still want the one study to be fairly strong, irregardless of the confirmatory evidence. I really have a lot of doubts about this study both from the blinding, the design of only having two active components, to think that it definitely shows that it has an effect on suicide, apart from showing that Clozaril is better than olanzapine for this indication.

DR. OREN: Dr. Katz.

DR. KATZ: I just want to sort of -- you seem to conclude that it shows that it's superior to olanzapine. Are your questions related to the fact that the unblinded nature of the data accrual make you question the reliability of that difference, and the fact that you're not sure whether or not Zyprexa patients -- I'm trying to understand your reasoning, it's very important to us.

DR. MALONE: I think it's everything put

together, that if you wanted to have confirmatory data and one well-controlled study, you'd want that study to be fairly definitive. And I think with questions about blinding and still in my mind with questions about not having a no-treatment group or -- I don't know how you would do that, maybe a community-control -- but without having that in the study, it's not a strong enough study to stand on its own as one single study. I'm not sure if I answered it.

DR. OREN: Dr. Ryan.

DR. RYAN: I think I come down in a somewhat different position, so let me sort of be long-winded about it. It seems like that the FDA and industry together made a plan for the study which was substantially carried out as planned, that there's a lot of decisions that went into a complex and ground-breaking study like this that one could make second-guesses on but none that I'm strongly urged to make a bad second-guess on, and certainly none of the decisions where you say, "Well, they snuck one over", and they weighed it in a way that's really going to be helpful to them. I mean, you know, the question of which blind rater to use, I would have made the decision the same way. I was personally convinced by the evidence that that was much better than a whole

bunch of separate blind psychiatrists.

The question of whether you could have really done it blind or not is an interesting question, you know, that people with more expertise in schizophrenia than I have suggested would be very hard to do blind. Perhaps we can say we do have a blind, but they seem to make a substantial argument that way.

So, I individually, separately, would say that this study was positive and done well and what they'd agreed to. And so for me, separately, the only one you're left with is the p-value that is certainly, you know, 1 chance in 33, so it's under the 1 chance in 20 that we arbitrarily say is significant, and yet not a .001 or something, not the numbing homerun that's separate, positively each separate site, and so then you're left with a very solid p-value, but not a .001. You may never be able to pat over a study so you get a .001 with a base rate on the phenomena here. And the separate question of how strong the other evidence is.

I actually would weigh on the whole enchilada of saying that the other evidence with one study, in my understanding of what you're saying, is enough, but certainly separately it seemed to be a well-designed, well carried out study where we could

make second-guesses, but not certainly ones that disturb me a bit.

DR. OREN: Dr. Cook.

DR. COOK: I realize there are problems with the Walker study, but this seemed to have been designed as a replication of a relatively solid piece of epidemiological work, so I do think the confirmatory evidence is not only there, but it preceded. And I sort of go along with what Neal is saying, essentially a shot was called. It was a reasonable shot, there was consultation with you, decision seemed reasonable, and that's the best you can do. There's clearly not a "well, the original call was negative, so we went back and found something that was positive" sort of thing.

DR. OREN: Dr. Winoker.

DR. WINOKER: I'm also of the mind to think that the previous "confirmatory" data is significant so that a study that we judge to be supportive would not be convincing here. Again, I'm mindful that this is a both very clinically important and challenging problem and a very difficult one to design and conduct a clinical trial in this era of increasing challenge, with all of the concern about protection of human subjects. I think that's just the

constantly evolving factor to address important clinical problems.

The main issue that I can see or understand -- and maybe some of our colleagues can sort of expand on this, or present some different perspectives in terms of the lack of blinding, which certainly make us all fell more comfortable -- relates to the question of under-referral of the Type 1 events in the subjects on Clozaril, and while I don't think we can have absolutely satisfactory clarification of that, I found myself reasonably persuaded that pretty legitimate efforts to investigate that and look systematically at sources of under-referral did not really support that. So I found myself being reasonably comforted or assured against the concerns about the lack of blinding and otherwise feeling persuaded that the data favoring Clozaril for suicidal behaviors, which I think are tangible and clinically meaningful events -- and, again, in the face of the overall evidence that olanzapine was producing clinically significant effects along other sort of standard criteria, plus I didn't see any evidence that that population was being undertreated, there was the question about whether they were almost on excessive adjunctive treatments, but they were certainly getting

aggressive treatment apparently to manage their clinical situation. So, I came out on the side of being persuaded by the evidence.

DR. OREN: Dr. Rudorfer.

DR. RUDORFER: I'm afraid I'm going to have to stay up the negative terrain. I was, on the whole, disappointed by this study. Aside from the blinding issue -- which, again, I think that if this were to be the single definitive trial, I think that should be a requirement. I find the concomitant medication treatment overwhelmingly troubling -- that is, we are not even able to see a subset of this population comparing the two active treatments head-to-head. We see comparisons of clozapine plus some other things versus Zyprexa plus a lot of other things, and those other things may have been beneficial, they may have been detrimental, I'm not sure we've fully resolved the dosing issue. It seemed that the clinicians in the Zyprexa group were forced to go beyond the protocol -- and I'm not sure that they all did. I mean, we saw -- we actually have the data on the patient deaths and, as I read the case reports, all of the patients in the Zyprexa group who died received no more than 20 mg a day of Zyprexa, so I'm concerned there that clinicians -- some clinicians

may have been reluctant to exceed that. And, again, the bottom line for me is that I would like to see, even in a subset of patients, a head-to-head comparison because I think that's what the study purports to be. So, I'm afraid I just don't find this evidence persuasive.

DR. OREN: Anyone else want to comment? Dr. Ortiz.

DR. ORTIZ: I guess since this is kind of a check-in, I think the way Dr. Winoker put it in terms of -- I think I am persuaded that suicidal behaviors were decreased and suicide was prevented in the study. I think I'm not as concerned about the blindedness because of the incredible co-morbidity and complicatedness of these patients, and I suppose a study could be designed that is able to do that, but I'm not sure about the safety and ethics of doing something like that.

I am still a little concerned about the implications from -- though I think Dr. Hamer has suggested that we've already got indications for symptoms in other medications, so suicidality isn't adding anything new in this -- though, for me, the concern is it's more -- it's associated with mood disorder. And then the treatment-resistance, I guess

that doesn't bother me as much as schizoaffective, which I'm still not convinced is well substantiated. But I guess just the question of suicidality in this particular population or this study, for me, the data is persuasive.

DR. OREN: On the specific subject of is a single randomized trial good enough, I keep getting pulled in each direction. One of the points I'm still wrestling with -- I don't know if the company has any thoughts on it -- the baseline level of suicide attempts or suicidality in the Clozaril group was higher than in the Zyprexa group -- I think it was about 3.7 incidence in each of those categories for the Clozaril group, and about 3.2 in the Zyprexa group. Could any of what we are seeing with the relative efficacy of Clozaril be a regression to the mean? If there were two studies up, I wouldn't be asking that question.

DR. RYAN: I was just mumbling that they didn't include that in the thing, so wouldn't that work against them rather than for them?

DR. OREN: If they were a sicker group, it would work against them. If just by the way time captured they, they were a totally equivalent group, that might work to their advantage.

DR. RYAN: How?

DR. OREN: By virtue that at the end of the study there would be a greater likelihood that all would have had a similar total number. If both drugs had no effect by the end of the study period, it's possible that the levels would have been the same in both groups, even if statistically one happened to be higher than the other at the beginning. Dr. Zaninelli.

DR. ZANINELLI: Just to remind the committee, this was a time-to-event, not a change-from-baseline analysis, so regression to the mean I don't think would apply here.

Also, looking at the difference in the mean number of lifetime suicides, lifetime hospitalizations to prevent suicide was at baseline. There wasn't statistical difference.

While I'm up here, I'd also like to address Dr. Wang's question regarding the psychopathology of the schizoaffective and schizophrenic subgroups. We've done the analysis in the mean time. Do we have a slide right now? That was quick.

(Slide)

We've shown in the overview slide

regarding the total score on the PANSS, it was about 85 overall. Actually, in the schizoaffective group it was about 81, in the schizophrenic closer to 85. The mean change from baseline was 20 and 21 points for schizoaffective disorder and Clozaril and Zyprexa, respectively, and 20 to 21 points in the schizophrenic group. So about the same baseline PANSS score in schizoaffective and schizophrenic patients, and pretty much the same change from baseline at endpoint. And that difference isn't statistically significant, less than .001.

Showing a comparable efficacy with respect to changes in psychopathology, as introduced by the PANSS.

(Slide)

Okay. Repeating what I said. Again, these are schizophrenic and schizoaffective patients in each subgroup -- schizophrenic patients, mean baseline PANSS total score, a little bit higher in the schizophrenic group, but the change from baseline around 20 in all four subgroups -- again, highly significantly different from baseline.

DR. OREN: Dr. Katz.

DR. KATZ: I would just say that it's an active control trial that doesn't show a difference

between treatments, it's hard to interpret that. I don't know if it's a critical point here, but I don't know what to make of it.

DR. OREN: So, again, is one study, or is this one study good enough to show what we need to show. Dr. Hamer?

DR. HAMER: I'm curious, does the sponsor have any other clinical trials of suicidality underway?

DR. ZANINELLI: No.

DR. OREN: Dr. Hamer, could I ask you to comment on whether the single trial you think would be adequate to support some kind of a claim?

DR. HAMER: I'm going to equivocate. If this were a blinded trial, I'd be really happy with it.

DR. OREN: Dr. Wang, do you want to comment on this?

DR. WANG: It puts a lot of pressure to make sure that the -- particularly the EPI -- the ERI study is methodologically rigorous, which it has its limits. And the overall much larger effect in the observational study suggests that there is some bias to it, but how much of it is potentially bias and how much of it is real effect is hard to say.

DR. OREN: Dr. Katz.

DR. KATZ: Do you want to take a view on whether or not the dataset, as it is, supports approval with the one study and confirmatory evidence standard?

DR. WANG: Okay, I'll take a stand. Given it's an epidemiologic study -- I'm talking about the ERI study now, and just focusing on, okay, you have one trial, you also have some observational EPI data, how good is that EPI data, and its okay, it has its limits. So I'll say as far as using non-RCD data, it's got its problems, but it's about probably the best you're going to do.

DR. KATZ: But that's only half the standard, that's the confirmatory evidence standard. The other part of the standard is whether or not the one trial that we have is robust enough to, in conjunction with the EPI study, make an approvable package.

DR. WANG: To some extent, the implications -- I'll give you an answer. To some extent, the question is -- we're being asked should the indication be enlarged because that will hinge on what our answer is to this. And in a sense, we're being asked to do a quick decision analysis in our

head and say, okay, what happens if this -- I mean, it's a much larger question.

I ultimately, doing my quick one in my head -- you know, quick decision analysis -- think that even if InterSePT is wrong, and let's say it's completely biased and this benefit we're seeing is just way off the mark and there's no benefit at all. I've been swayed by the kind of comments that Dr. Goldman was saying earlier, that in the face of a whole bunch of decreasing risks, potentially greater benefits such as the MED analysis, even if we're completely wrong, the expansion may not be that awful a thing. So, ultimately, I'm a little bit less perturbed by whether there's a chance that this is biased, a little bit less than I would be in another situation. So, it meets my standard, if that's --

DR. KATZ: I guess the question is whether it meets our standard.

(Laughter.)

Let me try and parse it out because it really is important for us to understand the thinking of all the committee members. Forget the standard, the one study plus confirmatory -- just put that -- let's not talk about that, but let's just talk about the study, the InterSePT study, and whether or not you

think it's a robustly positive study, with all its warts. Let me just ask you that simple -- well, it's not a simple question -- but that single question.

DR. WANG: It's not robustly positive, for all the reasons we've been talking about, but it is -- it's robust in the sense that there's so little -- if it's real, if it's not completely explainable by bias, then this is robust because there's so little to actually treat suicidality, and the effect size was actually impressive, you know, when you do the calculation. I saw your calculation. It's actually very impressive from a public health point of view. So, it has warts. It isn't maybe robust, in my typical use of the word robust, but maybe it's robust enough.

DR. OREN: Dr. Hamer.

DR. HAMER: I want to rephrase my vote. Assuming that the blinding issue does not bother the FDA, then I think this study had an impressive effect size, and I think the cumulative weight of the epidemiological studies that are out there paired with this are persuasive.

DR. KATZ: We're not going to get you to say whether or not the blinding upsets you very much, are we?

DR. HAMER: No, not at all.

(Laughter.)

DR. OREN: Jean Bronstein, you haven't commented recently.

MS. BRONSTEIN: I don't feel statistically up to the group here, but I really do think that the study has offered us something for this population that we really need to consider, and it may not be perfect, but I think my vote goes to offering this for the psychotic population.

DR. OREN: Has everyone addressed this specific question? Dr. Cook, did you?

DR. ORTIZ: Yes, I did.

DR. OREN: Okay. I think since the drug is already out on the market, the questions that arise are different perhaps than introducing something entirely new to the market. In that context, I think a single trial like this is good enough to support a claim focusing on suicidality, at least the schizophrenia. Do you want us to talk about --

DR. KATZ: I'm just wondering why the fact that it's already available affects your decision about what the standard ought to be.

DR. OREN: Well, I think relying on a single study puts a lot of eggs in one basket. I

think the fundamental question is when a drug is available, clinicians can use it in an off-label basis and will feel free to do so if the data is out there. And I think the -- from that perspective, the amount of data that the study provides to perhaps guide clinicians in using this for this indication would be useful to them, and I think it would be reasonable to have official imprimatur behind.

DR. LAUGHREN: Let me just comment that I see this situation as quite different than the usual situation where we borrow evidence from other data for a drug. For example, if we have acute efficacy data for an antipsychotic drug, we might be willing to rely on one trial for long-term efficacy. But I see this as a distinct claim. In fact, the evidence shows that there's a separation between the antipsychotic effect and the effect on suicidality.

DR. OREN: I think at least in terms of -- and this gets into specific wording -- but if for the claim of emergent suicidal ideation or emergent suicidality, that is something different than -- and this goes back to your question -- than lifelong treatment with that. I think this is an important clinical area where there isn't a good armamentarian to use, and therefore that increases the potential

urgency for considering this indication.

DR. LAUGHREN: I just want to make sure that what I'm hearing from -- when you say yes, you're basing your decision on the evidence in hand, what we have in front of us, the single study and whatever confirmatory evidence we have in hand to support this new claim.

DR. OREN: Do you want us to address specific language kind of questions now, or do you want us to turn to olanzapine?

DR. LAUGHREN: Why don't we talk about the olanzapine issue and how it should be thought of relative to olanzapine.

DR. OREN: Dr. Cook.

DR. COOK: Well, it seems to me there was a concerted deliberation about choosing a reasonable active comparator, and so I don't think you can make a statement about olanzapine. It could just as easily have been Resperidon (phonetic). The logic for choosing this one doesn't seem to be a reason to make -- I mean, obviously there's always a concern when you're comparing two things, one might have gotten worse, but all the evidence here suggests that clozapine was better, not that olanzapine is worse.

DR. OREN: Dr. Winoker.

DR. WINOKER: I'm not sure of your exact question, but something that was sent to us sort of posed three answers making specific reference to olanzapine, sort of extrapolating to all other atypicals, or just making a comment against standard treatment, and I would very much favor the third of those options. I think it's clearly problematic to try to extend from olanzapine to the whole broad category since, as Dr. Meltzer's comment, we're not sure of the subtle pharmacological differences that might play into this. So, to me, that would be the most appropriate.

DR. LAUGHREN: This relates very directly to the precise language we would use in describing both the trial and the claim in labeling, and the choices open to us are to -- in some cases, we've done this -- is to simply state that clozapine was superior to a standard drug. We wouldn't even have to mention the drug, even though many people would know what the drug was, and the claim itself would not need to say anything at all about a comparison, it would simply state that it has this benefit. So, that clearly is an option.

DR. WINOKER: And that's one that I would favor for the reasons I mentioned.

DR. OREN: Dr. Mehta.

DR. MEHTA: When you describe the study, I don't know how you're going to do it without putting the side-effect data, without putting the control agent name.

DR. LAUGHREN: Well, it will be a challenge for us, but it's something we've done in other settings. We have managed to describe comparisons without naming the comparator.

DR. OREN: Dr. Katz.

DR. KATZ: The question, I think, is whether or not the study, as conducted, truly demonstrates superiority to the comparator, in this case olanzapine. That's a difficult -- in general, in comparative studies, it's a difficult conclusion to draw largely because you have to worry about whether or not you really had a fair comparison to the comparator. In this study, you can think of it in worse case -- unless it made the patients worse -- but, barring that, you can think of it sort of as a placebo, and so you can conclude that the drug had an effect, but it's difficult typically in these sorts of studies to say that it was truly -- you know for a fact that it was better than the comparator, again, because the question of what's a fair comparison in

terms of dose of the comparator, and that sort of thing, is a complex issue. So, as Tom says, we have in the past not identified active controls in other settings.

DR. OREN: Ms. Bronstein.

MS. BRONSTEIN: I don't know whether this is valid, but it was interesting to me to note that the number of other drugs used with Zyprexa were much higher, and in managing patients that's more difficult. So, that impressed me that the Zyprexa was a more difficult drug to manage for this patient population.

DR. OREN: Dr. Wang.

DR. WANG: Another reason to think about not naming the comparator is -- I mean, in addition to just -- maybe there's a little bit making less of a definitive statement based on data that we might still harbor a little bit of doubt about. Another reason is just thinking about down the line for the practitioner who has a patient who is on olanzapine, who suicides or something. Does this box them in? Are they in legal difficulty because the clinician didn't have the patient on a regimen for high risk? If you name that comparator, you might get the physician in trouble.

DR. KATZ: I don't know if that's really

a consideration that we ordinarily think about here. Again, we generally decide whether or not the data support a particular claim, and if they do, they get that claim. If we think it's misleading to conclude that the investigational drug was better than the control, we won't put that, again, for reasons of interpretation of the trial, not so much because somebody might get into trouble if they do this or that.

DR. OREN: The most conservative thing to say is just that it's better than nothing. It treats --

DR. KATZ: As Tom points out, that's an option, not so much to say it's better than nothing, but just to say it's effective. I mean, that's typically how we decide whether something is effective.

DR. OREN: Dr. Ryan.

DR. RYAN: In all the evidence so far, we have no available data that suggests there's differential antisuicide over suicide-promoting, I guess, effects of the different atypicals and, indeed, no evidence that there's differential effects of the atypicals and the classic antipsychotics, right? So, given that, we simply think this was an exemplar of

the whole class, and that's the reason for not mentioning it? Because everything that was presented here -- and I'm not an expert in this area -- there's no evidence that one is better than another excepting clozapine.

DR. KATZ: Again, one option is that you would just -- since only olanzapine was studied, one option is to say Clozaril is better than olanzapine in preventing suicide. I mean, that's one reasonable option. That's ostensibly what was shown in the study. But what I'm saying is that we may be reluctant to do that because we're not sure that olanzapine was used -- besides the fact that it's unblinded and who knows how patients were actually dosed and what the motivation for dosing with a given drug was, given that the investigators had new-treatment assignment -- we don't know that it was a strictly fair comparison to olanzapine. So, that would be the reason for not mentioning it.

DR. RYAN: I was trying to agree with you, it's just that I gave such a long answer it was hard to know that I was agreeing.

(Laughter.)

But, in addition, it might be misleading to the practitioner to emphasize that one single

compound rather than the fact that this is probably better than a lot of them, or something.

DR. OREN: Dr. Katz, in your comment, you said that one is better than the other in preventing suicide. In fact, the data from the study did not show that, and I think that's why the language that is used here is critical to whatever we'd vote on in the end.

Anything else on the olanzapine question?

(No response.)

Do you want us to address the adequacy of suicidality outcome? Probably that's a key thing because that would be part of the language.

DR. KATZ: I think we've discussed that. I think most people have voted that this was -- the package is sufficient for approval, so I think that's covered.

DR. OREN: Do you want anything further?

DR. KATZ: I don't think so, other than to say thanks very much, it's obviously a very challenging issue, a lot of subtleties, and I appreciate very much your work on this.

Let me also just mention that this is Sandy Titus' last meeting as the Executive Secretary for this and for the PCNS Advisory Committee. She's

moving on to other things. She's done a tremendous amount of work for a number of years working with us, and we'll miss her, and thank you very much. Thanks for everything you've done.

(Applause.)

DR. OREN: This meeting is adjourned.

(Whereupon, at 3:15 p.m., the meeting of the Psychopharmacological Drugs Advisory Committee was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Psychopharmacological Drugs Advisory Committee Meeting

Before: FDA-CDER

Date: November 4, 2002

Place: Gaithersburg, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.